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The Impact of Current COVID-19 Therapeutics on Patients' Clinical Improvements Based on Disease Severity; A Systematic Review.

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Abstract:

Introduction: COVID-19 pandemic is not a new issue that encompasses the entire world. It is becoming increasingly urgent to find effective medications. This systematic review was conducted to discuss the clinical impact of some proposed managements against COVID-19.

Methods: PubMed, Scopus, Cochrane Library, Embase, and Google Scholar databases were searched from their inception to June 15, 2020, to identify studies reporting the current treatment process and medications for COVID-19.

Results: After searching databases, a total of 5450 articles were assessed. A number of 42 relevant studies were identified as eligible for the review including a total of 5599 patients. The severity of illness was investigated in 5053 cases including 3169 mild or mild to moderate or moderate, 222 moderate to severe, and 1662 severe cases. Among the therapeutics reported in these studies, 15 medications besides convalescent plasma showed some evidence of antiviral activity. Antivirals (34%; 14/42), especially lopinavir/ritonavir, were the main classes of therapeutic agents evaluated against COVID-19. Approximately, 14.3% (6/42) of the studies which assessed the impact of hydroxychloroquine and azithromycin, convalescent plasma therapy, lopinavir/ritonavir plus azithromycin, methylprednisolone, and interferon α-2b, have reported clinical improvement in all cases. A number of 10 studies (23.81%) exhibited a negative conversion of SARS-CoV-2 in all cases.

Conclusions: Based on our findings, considering the diverse and scattered effects of current medications on clinical outcomes and the rate of negative conversion of SARS-CoV-2, large clinical trials are required to evaluate the best treatment options for COVID-19.

Keywords: COVID-19; Clinical improvement; Medications; SARS-CoV-2; Systematic review

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1. Introduction

Novel Coronavirus Disease 2019 (COVID-19) outbreak occurred preliminary in China in December 2019 [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread through many countries rapidly so that it was announced as a pandemic on 11 March 2020 by the World Health Organization [2-5]. The virus has already infected nearly 8.2 million people worldwide resulted in 444,813 deaths as of June 18, 2020 [6]. The percentage of mortality attributed to COVID-19 decreased from 12.4% during week 22 to

7.3% during week 23 (June 11, 2020) but remained above baseline. The overall cumulative hospitalization rate is 89.3 per 100,000 population which is a huge burden on the healthcare system [7].

At the early stage of COVID-19 pandemic the major symptoms were fever and respiratory involvement. However, the symptoms pattern has gradually changed and gastrointestinal [GI] manifestations are more frequent these days [8, 9]. Based on identified pathogenesis, the virus might pass through the nasal and larynx mucous membrane and enters the lungs via the respiratory tract. Then it would enter the peripheral blood from the lungs and attack the organs expressing ACE2, such as the lungs, heart, kidneys, and gastrointestinal tract [10].

Unfortunately, at this time, there is no specific medication to manage patients infected with COVID-19. Besides the attempts made to introduce a new vaccine or therapeutic agent, many different clinical trials have been launched to evaluate the efficacy of different existing therapeutics like antivirals, antimalarials, immunomodulatory medications, stem cell therapy, convalescent plasma therapy and etc. [11-16]. Some of these trials have ended up with the beneficial effects on patients outcomes [11, 13, 17] and some did not [15, 18, 19].

In such a pandemic emergency situation, it is mandatory to provide a general overview of current management effectiveness to achieve the best strategy against COVID-19. Furthermore, SARS-CoV-2 is an RNA virus so that its fast mutation could result in a resistance phenotype which might be triggered by utilization of blind medications [20]. Thus rapid determination of the best clinical approach is necessary. In this study, we conducted a systematic review to discuss the clinical impact of well-done observational studies and clinical trials on COVID-19.

2. Materials *&* Methods

Ethical approval or patient consent was not required because the present study was a review of previously published articles.

2.1. Search strategy

The Cochrane protocol was used to conduct of systematic review [21] and search in databases was performed based on the PRISMA guideline (Figure 1) [22]. International databases consist of Scopus, PubMed, Cochrane, Embase, and google scholar were used to search of articles from their inception to June 15, 2020. The following keywords and MeSH terms consist of: “treatment” OR “therapy” OR “COVID-19 drug treatment” OR “COVID-19 serotherapy” OR “Hydroxychloroquine” OR “Antiviral Agents” OR “Immunomodulation” were combined with “COVID-19” OR “severe acute respiratory syndrome coronavirus 2”. The search strategy was attached in supplementary section. The reference list of all identified documents was scrutinized, due to identify additional potentially eligible studies.

2.2. Inclusion and exclusion criteria

All type of studies which explain the current treatment process and drugs for COVID-19 were selected to conduct this study. Meanwhile, studies with these characteristics were excluded: (a) duplicate publications (b) full text in non-English language (c) reviews, letters, case reports, conferences and correspondence (d) do not provided sufficient information on patient data or descriptive studies (e) recommendations and guidelines (f) about herbal medicine (g) about vaccines and (h) description on clinical and imaging findings. However, few articles which are still in press also selected for the review to meet the aim of this study. The steps taken to study selection are presented in Figure 1.

2.3. Data extraction and quality assessment

Data extraction forms including country, year, type of study, total number of cases, sex ratio, mean age, type of treatment provided, coexisting conditions, number of mild/moderate/severe cases, days from disease onset to clinical intervention, number of cases needed mechanical ventilation, number of cases need intensive care unit (ICU), number of cases with negative conversion, time to negative conversion, time to clinical improvement, and mortality were filled independently by three investigators. Discrepancies were resolved by consensus and the final decision made by the corresponding author. Clinical improvement was defined according to the seven-point ordinal scale as follows: 1, death; 2, receiving invasive mechanical ventilation; 3, receiving high-flow oxygen; 4, receiving low-flow oxygen; 5 or 6, breathing ambient air; and 7, discharge [23]. The severity of illness was defined in some studies based on diagnosis and treatment program for COVID-19 according to the following criteria: (a) respiratory distress, breathing frequency $\geq$ 30 breaths/min; (b) mean oxygen saturation $\leq$93% in resting state; (c) arterial blood oxygen partial pressure/oxygen concentration $\leq$300 mmHg (1 mmHg = 0.133 kPa) (d) shock, and/or combined failure of other organs that required ICU monitoring and treatment [17]. The methodological quality of the included studies was assessed independently by two reviewers using Cochrane's risk of bias tool for randomized clinical trials [24], Newcastle-Ottawa Quality Assessment Scale for controlled retrospective studies [25], and NIH Quality Assessment Tool for case series [26].

3. Results

3.1. Study characteristic

At the end of the search process, 5450 records were retrieved through Scopus, PubMed, Cochrane, Embase, and google scholar searching. After the removal of 1088 duplicated cases, 4362 records remained. At the next step, all the remained records were screened by investigators, and among them, 3221 studies were removed, because of their irrelevance with COVID-19 treatment. Of the 1141 records, 1099 studies were excluded due to reasons mentioned in Figure 1.

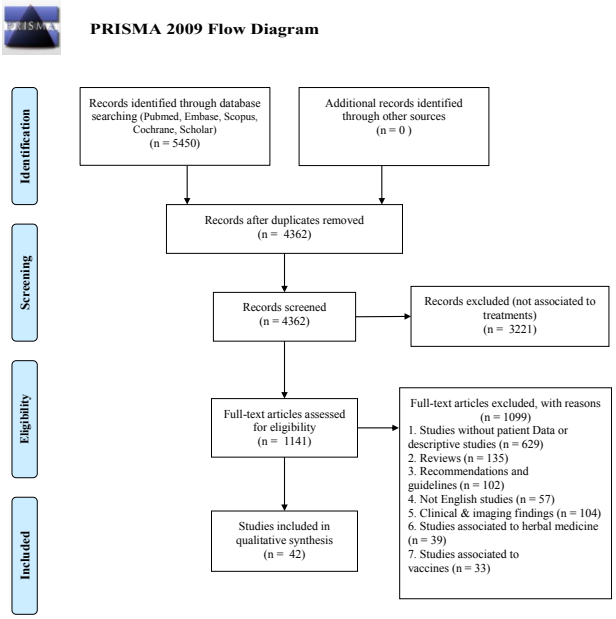

Figure 1. Flow diagram of the study selection process.

A total of 5599 patients in 42 included articles, were studied in this review. Figure 2 illustrated the frequency of patients received each therapeutic management. Hydroxychloroquine (HCQ) plus azithromycin (AZM) were prescribed in a large number of patients (n= 1921). The severity of illness was investigated in 5053 cases including 3169 mild or mild to moderate or moderate, 222 moderate to severe, and 1662 severe cases.

All selected studies described a total of 15 medications and convalescent plasma in different therapeutic categories that showed some evidence of clinical improvements and antiviral activity against SARS-CoV-2 (Table 1). The frequency of studies evaluated each therapeutic management was presented in Figure 3. Antivirals, especially lopinavir and ritonavir (LPV/r), were the most frequent studied classes of therapeutic agents (34%; 14/42). However, the efficacy of immunomodulatory medications (26%; 11/42), antimalarial agents (14%; 6/42), convalescent plasma (CP) therapy (14 %, 6/42), immunomodulatory plus antiviral medications (7%, 3/42), and antimalarial agents plus antiviral medications (5%; 2/42), was also investigated (Figure 3). Additionally, about 14.3% (6/42) of the studies showed clinical improvement in all cases [12, 27-31] containing the medications of HCQ and AZM (including 22 moderate patients), LPV/r plus AZM (including 35moderate patients), CP therapy (including 21 severe patients), Interferon alfa-2b (IFN-a2b)± Arbidol (including 141 mild to moderate), and Methylprednisolone (mPRED) (including 11 mild patients). The number of 10 studies (23.81%) exhibited negative conversion of SARS-CoV-2 in all cases [11, 12, 27, 29-35] containing the medications of HCQ and AZM (including 28 mild to moderate patients), CP therapy (including 21 severe patients), LPV/r plus AZM (including 35 moderate), Arbidol (including 40 mild to moderate), IFN-a2b±Arbidol (including 194 mild to moderate patients), Ruxolitinib (RUX) (including 20 mild to severe), and TCZ (including 21 severe patients) (Table 1).

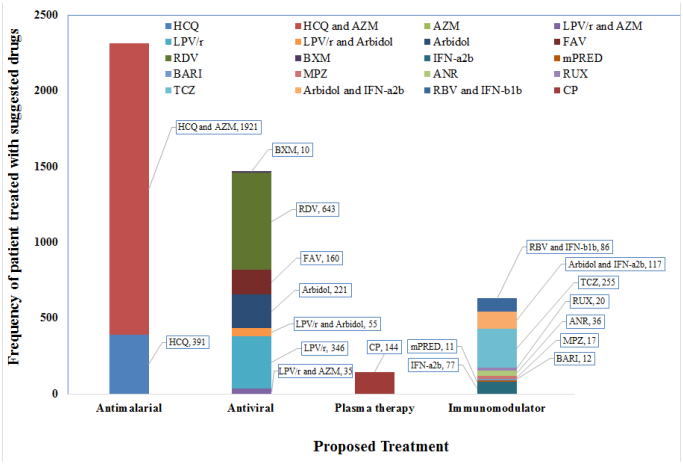

Figure 2. Frequency of patients received each therapeutic management. Digits indicate the number of patients.

HCQ: Hydroxychloroquine, AZM: Azithromycin, LPV/r: Lopinavir and Ritonavir, ARB: Arbidol, FAV: Favipiravir, RDV: Remdesivir, BXM: Baloxavir marboxil, RBV: Ribavirin BARI: Baricitinib, mPRED: Methylprednisolone, IFN-a2b: Interferon alfa-2b, IFN-b1b: Interferon beta-1b, MPZ: Meplazumab, ANR: Anakinra, RUX: Ruxolitinib, TCZ: Tocilizumab, CP: Convalescent plasma.

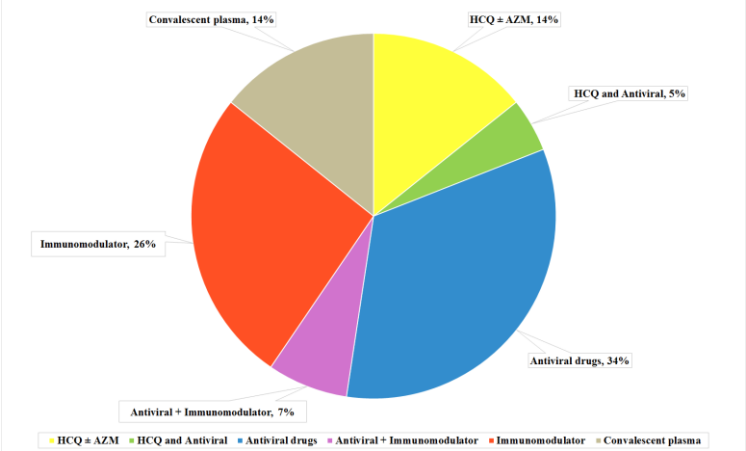

Figure 3. Percentage of studies evaluating each therapeutic management relative to 42 included studies.

3.2. Quality assessment

The quality of included clinical trial studies was moderate. The majority of clinical trial studies did not describe the randomization process and allocation concealment, moreover most of them were open-label. But outcome reporting was adequate. Some of included clinical trials were pilot studies and lack appropriate control group [23, 36, 37]. The quality of included case series and retrospective cohort studies were good and fair. The quality assessment tables and risk of bias graph for all included studies are available in the Supplementary Material.

4. Discussion

Despite the passage of several months after the SARS-CoV-2 outbreak, no effective treatment has been introduced, and there is conflict on the efficacy of proposed medications. In this review we considered the efficacy of available clinical approaches against COVID-19. We included 42 studies (19 interventional and 23 observational studies) which assessed the effectiveness of various medications like antimalarial agent, antiviral agents, immunomodulatory agents, and convalescent plasma therapy.

Among different clinical management reviewed in this study, antivirals were the most frequent clinical intervention assessed in 14 studies in comparison to standard treatment. Among them only two studies reported beneficial effect of RDV medications in severe patients [37, 38]. The observed relative ineffectiveness may originate from the partially long time between the onset of illness to treatment initiation, as the best time for antiviral therapy is at the initial stages of infection [39, 40]. Although, the U.S. Food and Drug Administration (FDA) announced an emergency use authorization (EUA) for the antiviral drug remdesivir in severe hospitalized patients with suspected or confirmed COVID-19 [41], but its efficacy is controversial [42]. Performing large randomized clinical trials with as short time as possible between the onset of illness to treatment in enrolling patients may reveal the actual efficacy of antiviral drugs.

Cytokine storm as a result of pro-inflammatory cytokines (TNF, IL-6, IL-1β) overproduction, could increase the risk of vascular hyper-permeability, multiorgan failure, and eventually death [43]. It was suggested that immunomodulatory agents could confront this condition [44]. Eleven out of 42 included studies investigated the effectiveness of immunomodulatory drugs which eight studies [13, 34, 35, 45-49] reported the beneficial effects of these agents. Dastan et al prescribed IFN-β-1a in combination with HCQ and LPV/r in 20 severe cases. According to their findings, there were no deaths or significant adverse drug reactions in the 14-day period and on day 10, 18 (90%) patients had negative RT-PCR samples and lung computed tomography recovery occurred after 14 days [50]. Combination therapy of IFN-β-1a or IFN-α-2b with HCQ or antivirals showed promising beneficial effects in patients with COVID-19 [27, 32, 50, 51]. Among six included studies evaluated tocilizumab (TCZ) efficacy, only one study reported that TCZ had no beneficial effects against COVID-19 [52]. Despite improvement in all cases, Zha et al., reported that the addition of corticosteroids to standard treatment did not make a significant difference between groups [28]. This may be due to the mild illness of investigated patients which led to recovery of all patients in both control and treatment groups. Although, the efficacy of immunomodulatory therapy in severe COVID-19 patients was reported [53]. It seems that future randomized clinical trials on immunomodulatory agents are valuable.

HCQ administration alone or in combination with AZM was the next frequent agent. It was suggested that antimalarial drugs such as chloroquine and hydroxychloroquine have beneficial effects in patients

with COVID-19 [54, 55], although some other studies reported not only the ineffectiveness of chloroquine or hydroxychloroquine but also their adverse effects in the patients with COVID-19 [18, 56]. A large clinical trial conducted by Mehra, R. Mandeep et al. showed that HCQ with or without macrolide was associated with no evidence of benefit, although the authors retracted their study [57]. In this review 8 out of 42 included studies evaluated the effectiveness of HCQ in patients with COVID-19 and among them five studies reported beneficial effect of HCQ with or without AZM [11, 31, 55, 58, 59]. However, the combination therapy with HCQ and AZM was suggested to be accompanied by some adverse effects especially prolonged QT interval [18, 60] which necessitate more consideration in the administration of these medications.

Six out of 42 studies (including 144 severe cases) assessed the beneficial effect of CP therapy, from which only one reported that CP therapy had no beneficial effect [61]. Additionally, three studies ended up with 100% improvement in severe patients [12, 29, 30]. Although, the sample size of CP therapy studies was small and four of them lack the control group. Therefore, large randomized clinical trials are mandatory to investigate the efficacy of CP therapy.

5. Conclusion

In such a pandemic emergency situation, a summary of current managements against COVID-19 could be helpful to provide an overview for researchers and clinicians. Based on our findings, antivirals especially LPV/r were the most frequent prescribed agents. However, HCQ and AZM, convalescent plasma therapy, and IFN-a2b showed promising clinical improvements against this coronavirus. Considering the diverse and scattered effects of current medications on clinical outcomes and rate of negative conversion of SARS-CoV-2, the outcomes of the ongoing clinical trials are urgently needed to evaluate the best treatment options for COVID-19.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020.
2. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020;368(6490):489-93.
3. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 2020.
4. Shah SGS, Farrow A. A commentary on" World Health Organization declares global emergency: A review of the 2019 novel Coronavirus (COVID-19)". International journal of surgery (London, England). 2020;76:128-9.
5. Lum LHW, Tambyah PA. Outbreak of COVID-19–an urgent need for good science to silence our fears? Singapore Medical Journal. 2020;61(2):55.
6. WHO. Coronavirus disease (COVID-19) outbreak situation [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
7. CDC. COVIDView, A Weekly Surveillance Summary of U.S. COVID-19 Activity [Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/pdf/covidview-05-15-2020.pdf.
8. Cipriano M, Ruberti E, Giacalone A. Gastrointestinal infection could be new focus for coronavirus diagnosis. Cureus. 2020;12(3).
9. Jin X, Lian J-S, Hu J-H, Gao J, Zheng L, Zhang Y-M, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69(6):1002-9.
10. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. Emerging microbes & infections. 2020;9(1):727-32.
11. Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents. 2020:105949.
12. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences. 2020;117(17):9490-6.
13. Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. The Journal of Infection. 2020.
14. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging and disease. 2020;11(2):216-28.

15. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine. 2020.
16. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020.
17. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020.
18. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. MedRxiv. 2020.
19. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, 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. Med Mal Infect. 2020;10.
20. Cao Y-c, Deng Q-x, Dai S-x. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Medicine and Infectious Disease. 2020:101647.
21. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):15-25.
23. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine. 2020.
24. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
25. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. Ottawa Health Research Institute: Ottawa, Ontario, 2010. 2015.
26. National Heart L, Institute B. Quality assessment tool for case series studies. National Institutes of Health. 2014.
27. Xu P, Huang J, Fan Z, Huang W, Qi M, Lin X, et al. Arbidol/IFN-α2b Therapy for Patients With Corona Virus Disease 2019: A Retrospective Multicenter Cohort Study. Microbes and Infection. 2020.
28. Zha L, Li S, Pan L, Tefsen B, Li Y, French N, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Medical Journal of Australia. 2020;212(9):416-20.
29. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. Jama. 2020;323(16):1582-9.
30. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. Journal of Medical Virology. 2020.
31. Kim MS, Jang S-W, Park Y-K, Kim B-o, Hwang T-H, Kang SH, et al. Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea. medRxiv. 2020.
32. Zhou Q, Wei X-S, Xiang X, Wang X, Wang Z-H, Chen V, et al. Interferon-a2b treatment for COVID-19. MedRxiv. 2020.
33. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. Journal of Infection. 2020.
34. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology. 2020.
35. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020;117(20):10970-5.
36. Perotti C, Baldanti F, Bruno R, Delfante C, Seminari E, Casari S, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial. medRxiv. 2020.
37. Antinori S, Cossu MV, Ridolfo AL, Rech R, Bonazzetti C, Pagani G, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post_treatment hospitalisation status. Pharmacological Research. 2020:104899.
38. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. New England Journal of Medicine. 2020;382(24):2327-36.
39. Stengler M. Nature's Virus Killers: M. Evans; 2001.
40. Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). Journal of internal medicine. 2020.
41. FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment 2020 [updated May, 1. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.
42. Ferner RE, Aronson JK. Remdesivir in covid-19. British Medical Journal Publishing Group; 2020.
43. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. The Lancet Respiratory Medicine. 2020.
44. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. International journal of antimicrobial agents. 2020.
45. Bian H, Zheng Z-H, Wei D, Zhang Z, Kang W-Z, Hao C-Q, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. MedRxiv. 2020.
46. Alattar R, Ibrahim TBH, Shaar SH, Abdalla S, Shukri K, Daghfal JN, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. J Med Virol. 2020.
47. Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. European journal of internal medicine. 2020.
48. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. Journal of medical virology. 2020;92(7):814-8.
49. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity reviews. 2020:102568.
50. Dastan F, Nadji SA, Saffaei A, Marjani M, Moniri A, Jamaati H, et al. Subcutaneous administration of interferon beta-1a for COVID-19: A non-controlled prospective trial. International Immunopharmacology. 2020;85:106688.
51. Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020;395(10238):1695-704.
52. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. European Journal of Internal Medicine. 2020.
53. Alijotas-Reig J, Esteve-Valverde E, Belizna C, Selva-O'Callaghan A, Pardos-Gea J, Quintana A, et al. Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. Autoimmunity Reviews. 2020;19(7):102569.
54. Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. Journal of medical virology. 2020.

55. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv. 2020.
56. H Decloedt E, Reuter H, Allwood B, Parker A, FN Koegelenberg C, Blockman M, et al. Benefit v. risk when usingchloroquine in patients with severe COVID-19 disease. SAMJ: South African Medical Journal. 2020;110(5):0-.
57. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet. 2020.
58. Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, et al. Full-length title: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel medicine and infectious disease. 2020:101738.
59. Gautret P, Lagier J-C, Parola P, Meddeb L, Sevestre J, Mailhe M, 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 infectious disease. 2020:101663.
60. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nature Medicine. 2020:1-2.
61. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. Jama. 2020.
62. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. Jama. 2020.
63. Hraiech S, Bourenne J, Kuteifan K, Helms J, Carvelli J, Gainnier M, et al. Lack of viral clearance by the combination of hydroxychloroquine and azithromycin or lopinavir and ritonavir in SARS-CoV-2-related acute respiratory distress syndrome. Annals of Intensive Care. 2020;10(1):1-3.
64. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. The American Journal of Pathology. 2020.
65. Ye X, Luo Y, Xia S, Sun Q, Ding J, Zhou Y, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020;24(6):3390-6.
66. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clinical Microbiology and Infection. 2020.
67. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. Journal of Infection. 2020.
68. Lan X, Shao C, Zeng X, Wu Z, Xu Y. Lopinavir-ritonavir alone or combined with arbidol in the treatment of 73 hospitalized patients with COVID-19: a pilot retrospective study. medRxiv. 2020.
69. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). MedRxiv. 2020.
70. Lou Y, Liu L, Qiu Y. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial. medRxiv. 2020.
71. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020.
72. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet Rheumatology. 2020.

Table 1. Data extracted from included papers. ST: Standard treatment, HCQ: Hydroxychloroquine, AZM: Azithromycin, LPV/r: Lopinavir and Ritonavir, ARB: Arbidol, FAV: Favipiravir, RDV: Remdesivir, BXM: Baloxavir marboxil, RBV: Ribavirin BARI: Baricitinib, mPRED: Methylprednisolone, IFN-a2b: Interferon alfa-2b, IFN-b1b: Interferon beta-1b, MPZ: Meplazumab, ANR: Anakinra, RUX: Ruxolitinib, TCZ: Tocilizumab, CP: Convalescent plasma, NR: Not reported.

Philippe Gautret (11)			**Wei Tang (18)**		**Zhaowei Chen (55)**		**First author**
20-Mar-20			7-May-20		10-Apr-20		**Year of study**
France			China		China		**Country**
Clinical trial			Clinical trial		Clinical trial		**Type of study**
HCQ+AZM	HCQ	ST	HCQ	ST	HCQ	ST	**Type of drug (Treatment)**
6	14	16	75	75	31	31	**Total number of cases**
47.5	52.8	37.3	48	44	44.1	45.2	**Mean age (Year)**
2.00	0.55	0.60	1.27	1.14	0.82	0.94	**Sex ratio (Male/Female)**
28 (77.78) mild/8(22.22) moderate			22 (14.67)mild/ 126(84) moderate/2(1.33) severe		62 (100) mild to moderate		**Number of mild/moderate/severe cases (%)**
4.3	3.9	3.9	16.6	16.6	NR	NR	**Days from disease onset to clinical intervention**
NR	NR	NR	28	17	NR	NR	**Coexisting conditions**
NR	NR	NR	NR	NR	NR	NR	**Number of cases needed Mechanical ventilation**
NR	NR	NR	NR	NR	NR	NR	**Number of cases needed ICU after treatment**
3	6	>6	8	7	NR	NR	**Number of days to negative conversion**
6 (100)	8 (57.14)	2 (12.5)	64 (85.33)	NR	NR	NR	**Number of negative conversion cases (%)**
NR	NR	NR	19	21	2.2	3.2	**Number of days to clinical improvement**
NR	NR	NR	45 (60)	50 (66.67)	25 (80.65)	17 (54.84)	**Number of clinically improved cases (%)**
0	NR	NR	NR	NR	NR	NR	**Mortality (%)**
HCQ administration could **significantly reduce** viral load in COVID-19 patients and its effect is strengthened by AZM.			The administration of HCQ **did not result** in a higher negative conversion rate **but more alleviation** of clinical symptoms than ST alone. HCQ administration is associate with some **adverse events**		Result showed that the use of HCQ could **significantly shorten** time to clinical recovery and promote the absorption of pneumonia.		**Outcome summary**

Sami Hraiech (63)			Philippe Gautret (59)	Matthieu Million (58)	li S. Rosenberg (62)			
24-May-20			11-Apr-20	1-May-20	11-May-20			
France			France	France	USA			
Retrospective			Case series	Case series	Retrospective			
LPV/r	HCQ + AZM	ST	HCQ + AZM	HCQ + AZM	AZM	HCQ+AZM	HCQ	ST
13	17	15	80	1061	211	735	271	221
62	60	60	52.5	43.6	NR	NR	NR	NR
2.25	7.50	2.75	1.16	0.86	1.74	1.53	1.34	0.99
145 (100) moderate to severe			69(92) mild/4(5.33) moderate/2 (2.7 severe	1008(95) mild/25(2.36) moderate/28 (2.64) severe	899 (65.96) mild/250 (18.34) moderate/214 (15.7) severe			
5	7	8	4.9	6.4	NR	NR	NR	NR
exist	exist	exist	49	474	39	125	54	33
12	16	15	12	NR	13	199	51	18
13	17	15	3	10	23	226	52	27
6	6	6	4	10	NR	NR	NR	NR
5 (38.46)	3 (17.65)	2 (13.33)	79 (98.75)	973 (91.71)	NR	NR	NR	NR
NR	NR	NR	4.1	10	NR	NR	NR	NR
NR	NR	NR	65 (81.25)	973 (91.71)	NR	NR	NR	NR
1 (7.69)	2 (11.76)	5 (33.33)	1 (1.25)	8 (0.75)	21 (9.95)	189(25.71)	54 (19.93)	28 (12.67)
Co-administration of LPV/r or HCQ+AZM **was not associate** with increased rate of viral clearance or SARS-CoV-2 PCR negativity			The results provided evidence of a **beneficial effect** of co-administration of HCQ and AZM in the treatment of COVID-19 and its potential effectiveness in the early reduction of contagiousness.	Administration of the HCQ and AZM combination before COVID-19 complications occur **is safe and associated with a very low mortality** rate in patients.	Treatment with HCQ, AZM, or both, compared with ST, was **not significantly** associated with differences in in-hospital mortality in patients with COVID-19.			

E. Salazar (64)	Mingxiag Ye (30)	Chenguang Shen (29)	Ling Li (61)		Kai Duan (12)		Min Seo Kim (31)		
27-May-20	15-Apr-20	27-Mar-20	3-Jun-20		22-Apr-20		18-May-20		
USA	China	China	China		China		Korea		
Case series	Case series	Case series	Clinical trial		Clinical trial		Retrospective		
CP	CP	CP	CP	ST	CP	ST	LPV/r + AZM	HCQ + AZM	ST
25	6	5	52	51	10	10	35	22	40
51	58	54	70	69	52.5	53	49	42.5	36.1
0.78	1.00	1.50	1.08	1.83	1.50	1.50	0.40	0.05	0.21
25 (100) severe	6 (100) severe	5 (100) severe	103 (100) severe		20 (100) severe		97 (100) moderate		
NR	32.3	18.2	27	30	16.5	NR	NR	NR	NR
16	2	1	exist	exist	4	6	8	5	9
17	NR	2	35	38	1	NR	NR	NR	NR
NR	0	NR	NR	NR	NR	NR	4	1	0
NR	4.3	7	3	3	3	NR	19.1	15.3	20.7
NR	6 (100)	5 (100)	41 (78.85)	15 (29.41)	10 (100)	NR	35 (100)	22 (100)	40 (100)
14	NR	12	28	NR	NR	NR	19.9	16.5	20.7
19 (76)	6 (100)	5 (100)	27 (51.92)	22 (43.14)	10 (100)	1 (10)	35 (100)	22 (100)	40 (100)
1 (4)	0	0	8 (15.38)	12 (23.53)	0	3 (30)	0	0	0
Administration of CP **is a safe treatment** option for those with severe COVID-19 disease.	This study revealed that CP therapy **is effective** against COVID-19.	Administration of CP **was associated with** improvement in clinical status.	CP therapy compared with ST, **did not result in a statistically significant** improvement in time to clinical Improvement.		This study showed CP therapy was well tolerated and **could potentially improve** the clinical outcomes.		HCQ with AZM **was associated with better** clinical outcomes compared to LPV/r with AZM or ST. The effect of LPV/r with AZM **was not superior** to ST.		

Qingxian Cai (17)		Ningfang Lian (66)		Xiaoting Ye (65)		Bin Cao (15)		Cesare Perotti(36)
18-Mar-20 China Clinical trial		21-Apr-20 China Retrospective		2020 China Clinical trial		20-Mar-20 China Clinical trial		29-May-20 Italy Clinical trial
FAV	LPV/r	Arbidol	ST	LPV/R	ST	LPV/r	ST	CP
35	45	45	36	42	5	99	100	46
43	49	58	63	NR	NR	58	58	63
0.67	0.87	1.65	0.89	1.00	0.25	1.60	1.44	1.55
80 (100) mild to moderate		30 (37.04) severe/ 51 (62.96) moderate		NR		199 (100) severe		46 (100) severe
7	7	10	13	NR	NR	13	13	NR
NR	NR	17	12	14	2	20	22	24
NR	NR	1	1	NR	NR	8	11	7
NR	NR	0	0	NR	NR	6 days	11 days	16
4	11	6	3	7.8	12	14	14	7
NR	NR	33 (73.33)	28 (77.78)	NR	NR	59 (59.60)	58 (58)	43 (93.48)
9	14	NR	NR	4.8	7.3	12	14	NR
32 (91.43)	28 (62.22)	NR	NR	NR	NR	78 (78.79)	70 (70)	NR
NR	NR	0	0	NR	NR	19.2 (19.39)	25 (25)	3 (6.52)
FPV showed **better therapeutic** responses on COVID-19 compared to LPV/r		Arbidol administration is **not associated** with improved outcomes in patients with COVID-19		The administration of LPV/r has a more **evident therapeutic effect** in lowering the body temperature and restoring normal physiological mechanisms		**No benefit** was observed with LPV/r treatment beyond ST.		Results indicate a promising **benefit of hyperimmune plasma** in Covid-19 patients.

Chang Chen (16)		Yueping Li (69)			Xiu Lan (68)		Lisi Deng (67)		Zhen Zhu (33)	
15-Apr-20 China Clinical trial		23-Mar-20 China Clinical trial			29-Apr-20 China Retrospective		6-Mar-20 China Retrospective		10-Apr-20 China Retrospective	
FAV	Arbidol	LPV/r	Arbidol	ST	LPV/r	Arbidol + LPV/r	Arbidol + LPV/r	LPV/r	LPV/r	Arbidol
116	120	21	16	7	34	39	16	17	34	16
NR	NR	52	49	41	59.5	52.3	41	47	40.5	26.5
1.03	0.74	1.10	0.78	1.33	0.48	2.00	0.78	1.43	1.43	0.60
209 (88.56) moderate / 27 (11.44) severe/		44 (100) mild to moderate			NR		33 (100) severe		50 (100) mild to moderate	
NR	NR	4.3	4.1	5.6	NR	NR	NR	NR	NR	NR
56	50	7	7	1	19	15	10	12	NR	NR
5	18	NR	NR	NR	NR	NR	0	0	NR	NR
NR	NR	NR	NR	NR	0	2	0	0	NR	NR
NR	NR	8.5	7	4	9.9	11.5	7	14	11.5	9.5
NR	NR	9 (42.86)	10(62.50)	5 (71.43)	33 (97.06)	36 (92.31)	15 (93.75)	9 (52.94)	19 (55.88)	16 (100)
7	7	NR	NR	NR	NR	NR	NR	NR	NR	NR
71 (61.21)	62 (51.67)	9 (42.86)	4 (25)	2 (28.57)	33 (97.06)	36 (92.31)	11 (68.75)	5 (29.41)	NR	NR
0	0	NR	NR	NR	1 (2.94)	1 (2.56)	NR	NR	NR	NR
Compared to Arbidol, FAV **does not significantly** improve clinical recovery rate of Day 7.FAV is associated with **significantly** shortened latency to relief for pyrexia and cough.		There were **no differences** between groups in the patients outcome.			There was **no significant** difference between patient received combination therapy (arbidol+LPV/r) and patients received monotherapy (LPV/r).		Arbidol plus LPV/r combination therapy may **be superior to** LPV/r monotherapy in treating COVID-19.		Arbidol monotherapy may **be superior to** LPV/r in treating COVID-19.	

J. Grein, N (38)	S. Antinori (37)	Jason D. Goldman (23)		Yeming Wang (71)		Yan Lou (70)		
10-Apr-20	11-May-20	27-May-20		29-Apr-20		5-May-20		
USA, Japan, Italy, France..	Italy	Germany, Hong Kong, Italy, USA, Singapore, Spain, Taiwan		China		China		
Case series	Clinical trial	Clinical trial		Clinical trial		Clinical trial		
RDV	RDV	RDV 10 days	RDV 5 days	RDV	ST	BXM	FAV	ST
53	35	197	200	158	78	10	9	10
64	63	62	61	66	64	53	58	46
3.08	2.89	2.08	1.50	1.29	1.89	2.33	3.50	2.33
53 (100) severe	35 (100) severe	397 (100) severe		236 (100) severe		NR		
12	11	9	8	11	10	12.7	8.5	13.6
36	19	exist	exist	112	55	5	4	4
8	35	43	25	28	10	NR	NR	NR
NR	18	NR	NR	NR	NR	1	2	0
NR	12	NR	NR	NR	NR	6	9	9
NR	21 (60)	NR	NR	NR	NR	7 (70)	7 (77.78)	10 (100)
28	28	14	14	28	28	14	14	15
36 (68)	20 (57.14)	107 (54.31)	129 (64.5)	103 (65.2)	45 (57.69)	6 (60)	5 (55.56)	5 (50)
7 (13.21)	9 (25.71)	21 (10.66)	16 (8)	22 (13.92)	10 (12.82)	NR	NR	NR
In this cohort, clinical recovery was observed in 68% of patients treated with RDV	RDV can **benefit** patients hospitalized outside ICU where clinical outcome was better.	There was **no significant** difference between a 5-day course and a 10-day course of RDV.		RDV was **not associated** with statistically significant clinical benefits.		There was **no significant difference** in patient outcomes between groups received BXM or FAV or ST.		

Lei Zha (28)		Ping Xu (27)		Qiong Zhou (32)			Ivan Fan-Ngai Hung (51)	
9-Mar-20		20-May-20		15-May-20			8-May-20	
China		China		China			Hong Kong	
Retrospective		Retrospective		Retrospective			Clinical trial	
mPRED	ST	Arbidol+IFN-a2b	IFN-a2b	Arbidol+IFN-a2b	IFN-a2b	Arbidol	IFN-b1b+LPV/r+RBV	ST (LPV/r)
11	20	71	70	46	7	24	86	41
53	37	50.9	53.2	40.4	41.3	64.5	51	52
2.67	1.50	1.37	0.89	0.77	0.00	0.85	1.10	1.28
31 (100) mild		56 (39.71) mild/82 (58.15) moderate/3 (2.13) severe		NR			NR	
4	4	NR	NR	17	8	8	5	4
3	8	13	20	7	1	14	75	46
NR	NR	0	0	0	0	0	3	3
NR	NR	NR	NR	0	0	0	NR	NR
15	14	24.2	27.1	20.3	21.1	27.9	>7	>7
NR	NR	71 (100)	70 (100)	46 (100)	7 (100)	24 (100)	12 (13.95)	12 (29.27)
8	6.5	NR	NR	NR	NR	NR	4	8
11 (100)	15 (75)	71 (100)	70 (100)	NR	NR	NR	NR	NR
0	0	0	0	0	0	0	0	0
There was **no association** between corticosteroid treatment and virus clearance time, hospital length of stay, or duration of symptoms.		There were no significant differences between two groups, although the absorption of pneumonia in the combined group was faster.Arbidol+IFN-2 b therapy can be used as an **effective** method to improve the COVID-19.		Treatment with IFN-a2b with or without arbidol **significantly** reduced the duration of detectable virus compared to group received arbidol.			The combination group (IFN- b1b+LPV/r+RBV) had a **significantly shorter** time to negative conversion than ST (LPV/r) group.	

Yang Cao (34)		Giulio Cavalli (72)			Huijie Bian (45)		Fabrizio Cantini (13)	
19-May-20		7-May-20			24-Mar-20		16-Apr-20	
China		Italy			China		Italy	
Clinical trial		Retrospective			Clinical trial		Clinical trial	
Rux	ST	ANR low dose	ANR high dose	ST	MPZ	ST	BARI	ST
20	21	7	29	16	17	11	12	12
63	64	68	62	70	51	64	63.5	63
1.50	1.33	2.50	4.80	7.00	1.83	0.83	5.00	5.00
32 (78.05)mild/7 (17.07) moderate/2 (4.88)severe		52 (100) moderate to severe			NR		24 (100) moderate	
20	22	NR	NR	NR	NR	NR	6	4.5
14	13	exist	exist	exist	9	4	10	12
2	7	NR	7	1	NR	NR	NR	NR
0	3	0	0	0	NR	NR	0	4
13	12	NR	NR	NR	3	13	NR	NR
20 (100)	21 (100)	NR	NR	NR	16 (94.11)	6 (54.54)	NR	NR
12	15	NR	21	21	28	28	<14	>14
18 (90)	18 (85.71)	NR	21 (72)	8 (50)	16 (94.12)	6 (54.55)	7 (58.33)	1 (8.33)
0	3 (14.29)	NR	3 (10.34)	7 (43.75)	0	0	NR	NR
RUX recipients showed **significantly faster** improvement in the chest CT at day 14 compared to the control group. The 28-day mortality was 14.3% in the comparison group. **No death** or deterioration occurred in RUX recipients		Treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients (**Not significant** compared to ST). There was **significant difference** in mortality between High dose ANR treated group and ST.			MPZ **efficiently improved** the recovery of patients with SARS-CoV-2 pneumonia with a favorable safety profile.		BARI therapy **significantly** improved the clinical and laboratory parameters. None of the patients required ICU support, and the majority of the patients were discharged.	

Xiaoling Xu (35)	P. Toniati (49)	P. Luo (48)	C. Campochiaro (52)		Ruggero Capra (47)		R. Alattar (46)
29-Apr-20	3-May-20	26-Mar-20	22-May-20		13-May-20		5-May-20
China	Italy	China	Italy		Italy		Qatar
Case series	Case series	Case series	Retrospective		Retrospective		Case series
TCZ	TCZ	TCZ	TCZ	ST	TCZ	ST	TCZ
21	100	15	32	33	62	23	25
56.8	62	73	64	60	63	70	58
6.00	7.33	4.00	9.67	4.50	2.50	0.37	11.50
21 (100) severe	NR	2 (13.3) moderate/ 13 (86.7)severe	65 (100) severe		NR		25 (100) moderate to severe
NR	12	NR	NR	NR	NR	NR	7
21	66	10	20	20	44	22	20
3	100	NR	4	2	5	4	7
NR	46	NR	32	2	NR	NR	25
NR	NR	NR	NR	NR	NR	NR	NR
21 (100)	NR	NR	NR	NR	NR	NR	NR
5	10	NR	28	28	12.5	8	NR
19 (90.48)	77 (77)	10 (66.67)	22 (68.75)	20 (60.6)	NR	NR	NR
0	20 (20)	3 (20)	5 (15.63)	11 (33.3)	2 (3.23)	11 (47.83)	3 (12)
TCZ, which **improved** the clinical outcome immediately in severe and critical COVID-19 patients, is an **effective** treatment to reduce mortality.	The response to TCZ was rapid, sustained, and associated with **significant** clinical improvement.	TCZ appears to be an **effective treatment** option in COVID-19 patients with a risk of cytokine storms.	clinical improvement and mortality were **not statistically** different between TCZ and ST groups.		Patients receiving TCZ showed **significantly** greater survival rate as compared to ST.		TCZ was associated with **dramatic decline** in inflammatory markers, radiological improvement and reduced ventilation support requirements.