Philippine Society of Allergy, Asthma and Immunology, Inc.

A REVIEW OF IMMUNOMODULATORS AS THERAPEUTIC INTERVENTIONS FOR MODERATE TO SEVERE COVID-19 INFECTIONS (April 20, 2020)

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Overview

The pandemic outbreak of the coronavirus disease continues to spread all over the world. Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Majority of patients present with mild symptoms. However, 14% may present with severe disease with a 3% to 5% mortality rate.[2] Drugs or biologics have not been proven to be consistently effective in the treatment of the cytokine storm seen in those presenting with severe disease. Cytokine storm syndrome (CSS) or cytokine release syndrome (CRS) refers to a group of severe hyper-inflammatory disorders which are part of the spectrum of hemophagocytic lymphohistiocytosis (HLH). Primary HLH have a genetic basis, while secondary or acquired HLH are induced by infections, malignancies and autoimmune diseases. In the context of rheumatologic disease, systemic hyperinflammatory states are called macrophage activation syndrome (MAS).[3] Clinically, it commonly presents as systemic inflammation with multiple organ failure, and high inflammatory parameters.[4]

Immunomodulators are agents which are used to modify the immune response to another level of activity by increasing (immunostimulation/immunopotentiation), decreasing (immunosuppression) or inducing immunologic tolerance.[5] For the COVID-19 cytokine storm, the immunosuppressants are being used to help regulate or normalize the over-active immune system.[6] Immunosuppressants used for infection-related inflammatory conditions may be categorized into pathogen-specific (i.e. antibody preparations, vaccines, etc.) or nonspecific pathogen immunosuppressive modalities (i.e. corticosteroid, targeted monoclonal antibodies, etc.).

This global pandemic has resulted in the off-label or compassionate-use therapy of a number of drugs. This review is done by immunologists to aid the clinician in making decisions based on evidence regarding which immunomodulator might best fit his/her COVID-19 patient and hopefully improve clinical outcomes and chances of survival. This review provides a comprehensive discussion on the different immunomodulators that may be considered for the treatment of the COVID-19 cytokine storm with consideration of:

a) mechanisms of actions of the immunomodulator
b) efficacy for treatment of COVID 19 cytokine storm
c) dose and timing of administration
d) safety profile of each immunomodulator

Understanding the pathophysiology of COVID-19 is imperative for the clinician to provide timely and appropriate treatment for each patient. Siddiqi and Mehra proposed a 3-stage classification of disease progression with distinct clinical findings, response to

therapy and clinical outcomes.(Figure 1)[7] Stage 1 is the Early infection (mild) stage, wherein the virus gains entrance to the body, incubates and attaches to the angiotensin converting enzyme receptor 2 (ACE2) which is also the SARS-CoV-2 receptor. These are found in lung, intestinal, and vascular epithelia. There is a rapid viral replication in the cells with eventual apoptotic (non-inflammatory) and pyroptotic (inflammatory) cell death targeting the T and B lymphocytes. This explains the lymphopenia noted at this stage which can contribute to decreased viral clearance and worsening of disease.

These reactions can lead to localized tissue damage and activation of chemokine and cytokine pro-inflammatory mediators which ushers in Stage 2 (moderate) presenting as pulmonary involvement without (IIa) and with (IIb) hypoxia. During this stage, the patient develops viral pneumonia and the inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin can be elevated.

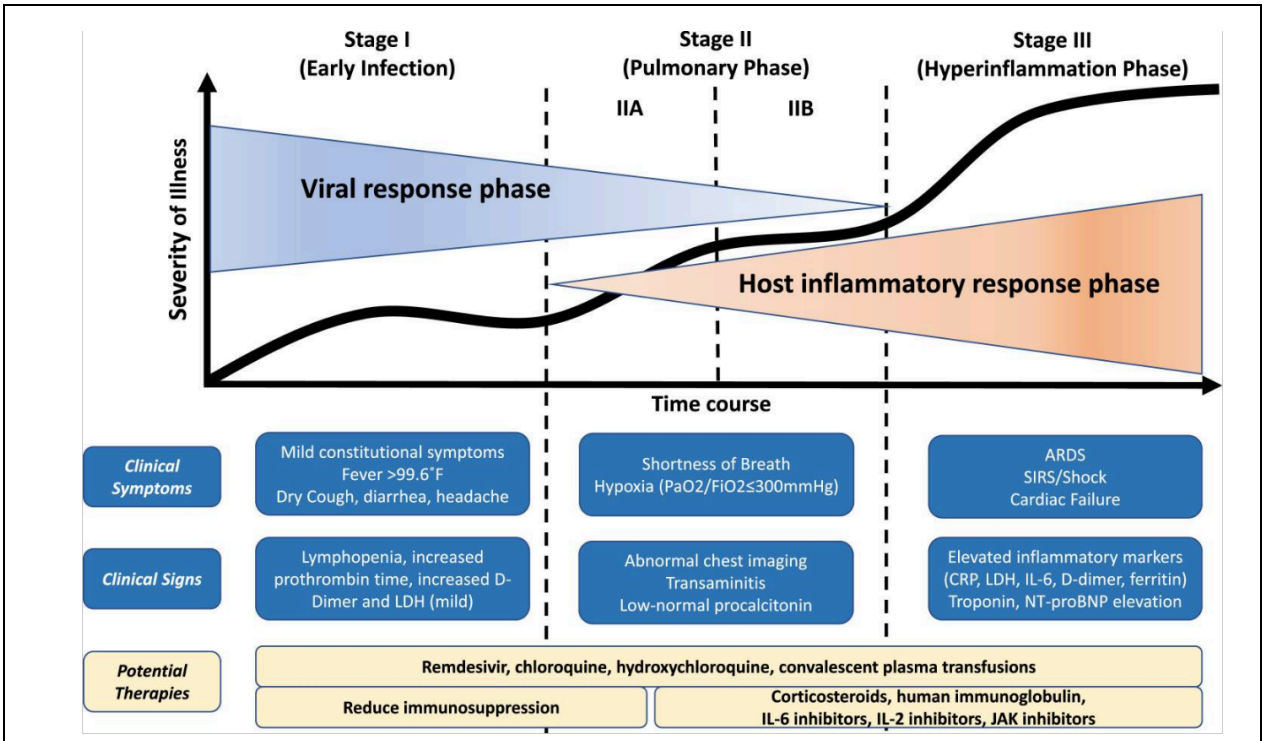


Figure 1. Classification of COVID-19 Disease States and Potential Therapeutic Targets
The figure shows 3 escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome, CRP=C-reactive protein; IL = Interleukin; JAK = Janus Kinase; LDH = Lactate dehydrogenase; SIRS = Systemic inflammatory response syndrome. [7]

Viral neutralizing antibodies (vNAB) are developed which should prevent viral endocytosis into cells and enable clearance of virus. However, in some individuals, vNAB can attach to Fc receptors on macrophages/monocytes leading to antibody-dependent enhancement of viral activity. This phenomenon leads to suboptimal anti-viral clearance, persistent viral replication and inflammation.[8]This stage occurs around

7–14 days after the onset of the symptoms when the virus starts a second attack. Clinically, this is characterized by worsening of symptoms with dyspnea, worsening of pulmonary lesions and development of hypercoagulable state with ischemic changes such as ecchymosis of the fingers and toes together with the worsening of heart and kidney functions. Inflammation, infection and other factors can lead to excessive activation of coagulation.

A minority of patients may progress to the third, more severe stage presenting with systemic hyperinflammation due to a cytokine storm. It has been likened to the phenomenon seen in secondary HLH wherein an overwhelming inflammatory reaction initiated by certain viral and bacterial infections (i.e., EBV, CMV, influenza, group A strep and other coronaviruses (MERS-COV, SARS) leads to organ damage and possibly death.[3] A balance of inflammatory and anti-inflammatory cytokines must be present in an individual for homeostasis and health. In cytokine storm due to SARS-CoV-2 infection, the hyper-inflammation that occurs during this stage has been associated with acute lung injury and increased mortality rate.

In a recent article in *The Lancet*, Huang et al studied the clinical features of 41 patients infected with 2019 novel coronavirus needing admission in a designated hospital in Wuhan, China.[9] These patients were noted to have high amounts of IL1B, IFNγ, IP10, and MCP1, probably leading to activated T-helper-1 (Th1) cell responses. Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα than those not requiring ICU admission, suggesting that the cytokine storm was associated with disease severity.[9] This also implies that several cytokines may need to be targeted when trying to control the cytokine storm.

The cytokine storm can progress in stages. In the early stage of infection, there is an elevated amount of IL-1 beta and tumor necrosis factor (TNF). They proliferate in the early minutes to a few hours of infection. This acute response triggers the proliferation of IL-6 and IL-18 which promotes a more sustained pro-inflammatory state. IL-10 appears later causing a negative feedback to IL-6. The Il-10 reaction is the body's attempt to control inflammation and is also termed "immunoparalysis".[8] However, it has been suggested that patients who survive the initial cytokine storm but subsequently die may be those who do not recover from immunoparalysis. This may be genetically determined.[10] When this happens, antiviral therapies may no longer be effective and immunotherapy via immunomodulation of the host response may be necessary to reverse the ongoing inflammation. Immunomodulation must, then, be instituted early enough to prevent the cytokine storm.

Some parameters may indicate the onset of the cytokine storm in COVID-19 infections. It is proposed that early initiation of immunomodulation during the period preceding the cytokine storm will lead to more successful treatment outcomes. In a retrospective study of 11 critically ill Chinese patients with COVID pneumonia, the following were noted to be high risk factors of cytokine storm:[11]

1) 50% or greater area of lung injury
2) Decreased CD4 and CD8 T lymphocyte counts (lower than 50% of minimum normal range values)

3) Increased levels of IL-6

The following parameters may also be used to decide whether immunomodulatory treatment for cytokine storm may be necessary:

1) Increasing ESR levels
2) Increasing ferritin levels
3) Decreasing platelet counts

There are several immunomodulators which can potentially control viral-induced cytokine storms, such as that induced by COVID-19 infection. Although all are still investigational, a few of these immunomodulators are already being used in clinical practice due to the urgent need to treat (manage) the cytokine storm.

REFERENCES:

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5(4):536-44 in BMJ Best Practice.
2. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
3. Minoia F, Davi S, Alongi A, et al. Criteria for cytokine storm syndromes. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. p.61-79.
4. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393. doi: 10.1016/j.clim.2020.108393. [Epub ahead of print]
5. Nelson RP, Ballow M, Bellanti JA. Advances in clinical immunomodulation: In Immunology IV Clinical Applications in Health and Disease. Bellanti, JA (ed) Bethesda, Maryland: I care Press, 2012. pp. 389-422
6. Pirofski LA, Casadevall A. Immunomodulators as an antimicrobial tool. Current Opinion in Microbiology 2006;9 :489-495.
7. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020. doi: 10.1016/j.healun.2020.03.012. [Epub ahead of print].
8. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. doi: 10.1007/s12250-020-00207-4. [Epub ahead of print].
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497–506.. doi: 10.1016/S0140-6736(20)30183-5.
10. Schulert GS, Zhang K. Genetics of acquired cytokine storm syndromes. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. p.113-130.
11. Favalli EG, Ingegnoli F, De Lucia O et al. COVID-19 Infection and rheumatoid arthritis: faraway, so close. Autoimmunity Reviews. 2020; 19: 102523. doi.org/10.1016/j.autrev.2020.102523

IMMUNOMODULATORS for COVID-19 CYTOKINE STORM

A. Pathogen-specific Immunomodulators (Polyclonal antibody-based agents)
   1. IVIG
   2. Convalescent plasma
   3. Hyperimmune globulin

B. Non-pathogen-specific immunomodulators
   1. Corticosteroids
   2. Hydroxychloroquine & Chloroquine
   3. Macrolides (Azithromycin)
   4. Targeted Monoclonal antibodies (Cytokine Antagonists)
      a. Anti-IL-6 (tocilizumab, siltuximab, sarilumab)
      b. Anti-IL-1 (anakinra, rilonacept, canakinumab)
      c. Anti-TNF (adalimumab)
      d. IFNα
   5. Anti-viral agents (arbidol, favipiravir, lopiravir/ritonavir, remdesivir, ribavirin)
   6. JAK-1 inhibitors (baracitinib)
   7. CCR-5 inhibitors (leronlimab)
   8. Stem cell therapy
   9. BCG vaccines
   10. Supplements
      a. Vitamin C
      b. Zinc
      c. Melatonin
      d. Quercetin

PATHOGENIC-SPECIFIC IMMUNOMODULATORS

POLYCLONAL ANTIBODY BASED AGENTS

The polyclonal antibody preparations contain antibodies that have different specificities in terms of the different epitopes on the virus. These will have neutralizing as well as non-neutralizing antibodies. They are then distinguished from each other by the concentration of neutralizing antibodies found in each preparation, namely:

a) Intravenous Immunoglobulin (IVIG)
b) Convalescent Plasma
c) Hyperimmune Globulin

1. INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Introduction

Intravenous immunoglobulin (IVIG) is a plasma product consisting primarily of immunoglobulin G (IgG) pooled from more than 10,000 human donors. Although used for immunoglobulin (IgG) replacement for Primary Immunodeficiency Diseases, at higher doses, it has an anti-inflammatory and immunomodulatory effect for various autoimmune or auto-inflammatory conditions.[1]

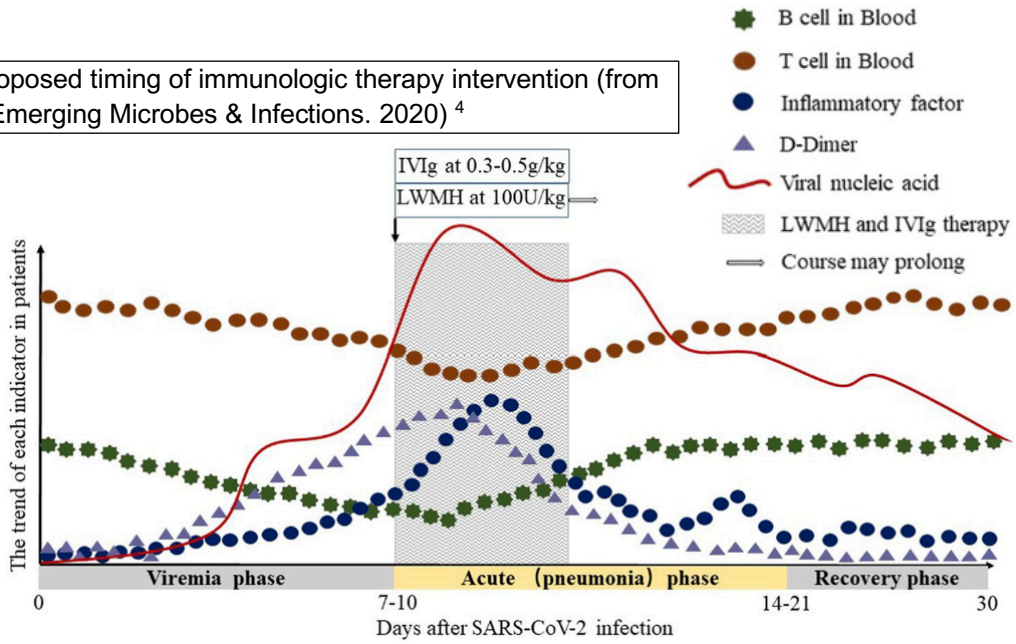
Mechanism of action and effect on COVID-19 infection

The mechanisms for its immunomodulatory effect are complex. These include modulation of antibody receptor expression and functions, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies, modulation of dendritic cell, T and B cell activation, differentiation, and effector functions. In vivo, a major mechanism by which IVIG exerts its anti-inflammatory effects is through the modulation of TH1 and Th2 cytokine and cytokine antagonist production.[2]

IVIG has been noted to reduce the levels of circulating IL-1β, increases levels of IL-1 receptor antagonists by 1000X and inhibits TNF-α mediated cytotoxicity in patients with other inflammatory conditions; hence it may have a role in controlling the initial phase of the cytokine storm in COVID-19 infection in adjunct with systemic anti-inflammatory agents such as corticosteroids.[3]

It is theorized that IVIG would be best given between day 7 to 14 or during the acute (pneumonia) phase to enhance the immune system (Figure 2).[4] It is during this critical period that the immune system could be overwhelmed and pushed to a severe disease progression.

Figure 2. Proposed timing of immunologic therapy intervention (from Lin L, et al. Emerging Microbes & Infections. 2020) [4]



Efficacy Studies of IVIG in COVID-19 Infections (Appendix A)

There is limited evidence of IVIG for COVID-19 infections. Present evidence points to some benefit of IVIG if given on the first sign of respiratory deterioration; however, these findings were based on expert opinion and low-quality evidence (case report and case series). A multi-center retrospective cohort study done in China found no significant difference in the 28-day and 60-day mortality between the IVIG and non-IVIG groups but in its subgroup analyses, patients with critical type illness had significant reduction in the 28-day mortality but not the 60-day mortality. There was also significant reduction in the 28-day and 60-day mortality with IVIG dose >15 g/day. Sixty-day mortality was reduced by using IVIG in the early stage (≤7 days from admission).[5] A prospective cohort study by Zhou et al. involving 10 COVID-19 patients showed improvement after giving moderate-dose corticosteroid and IVIG treatment.[6] Currently, there is one single-center, randomized, open-label, controlled study in China (NCT04261426) and one randomized, placebo-controlled, parallel study in France for COVID-19 ARDS which aims to look at the value of early treatment (NCT04350580).

Dose and Timing of Administration

1. IV Immunoglobulin (IVIG) for is given as adjunctive treatment in COVID-19 patients at the first sign of respiratory deterioration:
    a. Dyspnea; or
    b. RR > 30/min; or
    c. SpO2 < 93%; or
    d. PaO2/FiO2 < 300; or
    e. Progression of lung infiltrates > 50% within 24-48 hours.[7]

2. Suggested IVIG dose is: 0.3-0.5 g/kg/day for 5 consecutive days. Start infusion at 30 ml/hr (0.5 ml/kg/hr), doubling rate every 15 minutes up to a maximum rate of 100 ml/hr. Consider rate and dose adjustments based on renal and cardiac status.[7]

Adverse Reactions

Adverse reactions to IVIG are reported to occur in up to 5% to 15 % of all IVIG infusions and to affect 20% to 50% of individuals receiving IVIG.[8] Most of these reactions are mild, transient and reversible (flu-like symptoms, flushing, nausea, fatigue, fever, chills, malaise, and lethargy) and always occur within the first hour of infusion. Potentially serious reactions occur in 2% to 6% of patients and are rare such as anaphylaxis (in IgA-deficient patients), thromboembolic events, renal impairment, or severe hemolysis.

The majority of these symptoms are associated with rapid infusion and develop during the initial period of infusion which may be addressed by slowing down or stopping the infusion. Premedication is not a requirement for IVIG infusion; however, in some patients, acetaminophen, diphenhydramine or alternatively a non-sedating antihistamine and/or hydrocortisone one hour before the infusion may be given. Patients at increased risk of thromboembolic complications, or who have had prior thromboembolic complications, may benefit from additional preventive measures including pre-infusion hydration, low molecular weight heparin and use of low osmolality products. Rarely, acute kidney injury may occur with sucrose-containing products and careful evaluation and monitoring of renal function maybe necessary.[8] Routine serum IgA level testing in individuals without specific risk factor for IgA deficiency is not recommended. Importantly, IgA deficiency is not a contraindication to IVIG administration.[9,10]

Conclusion:

The use of IVIG may be beneficial when used early in the course of illness but this needs to be validated through clinical trials. Majority of the data comes from observational studies and expert opinion. The decision to use IVIG for COVID-19 must take into consideration the risks mentioned above versus the benefit of this agent, as well as the cost of treatment.

REFERENCES:

1. De Ranieri D. Intravenous immunoglobulin and its clinical applications. Pediatr Ann. 2017; 46:e6-7.
2. Negi V-S, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol. 2007; 27:233-45.
3. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020 (cited 2020 Mar 29) Available from: https://link.springer.com/1-.1007/s12250-020-00207-4.
4. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection --- a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020; 1-14.
5. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: a multi-center retrospective cohort study. medRxiv preprint. doi: https://doi.org/10.1101/2020.04.11.20061739.
6. Zhou ZG, Xie SM, Zhang J, et al. Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses COVID-19 patients who have failed low-dose therapy. Preprints 2020, 2020030065. doi: 10.20944/preprints202003.0065.v1.
7. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patient with Coronavirus Disease 2019. Open Forum Infect Dis. 2020; Available from: https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofaa102/581-740. Accessed 29 March 2020.
8. Perez EE, Shehata N. Intravenous immune globulin: adverse effects. Available from: https://www.uptodate.com/contents/intravenous-immune-globulin-adverse-effects?source=mostViewed_widget. Accessed on: 29 March 2020.
9. Dantal J. Intravenous immunoglobulins: in-depth review of excipients and acute kidney injury risk. Am J Nephrol. 2013;38:275-84.
10. Stiehm ER. Adverse effect of human immunoglobulin therapy. Transfus Med Rev. 2013;27:171.

2. CONVALESCENT PLASMA

Introduction

The difference between IVIG and convalescent plasma (CP) is that the former comes from a plasma pool donated by thousands of normal donors in a specified population while the latter is collected from the blood of donors who have recovered from the target disease. By doing so, a high titer of neutralizing antibodies specific to the infectious agent that caused the disease is obtained. Based on meta analyses on the Spanish flu pandemic of 1918, giving of CP became a candidate for prevention of disease in a pre-symptomatic exposed patients or as active treatment for patients who already have the disease.[1]

Mechanism of Action

In all passive antibody preparations, several types of binding antibodies are produced. Some will bind with an antigen to create an antigen–antibody complex that other cells of the immune system will recognize and destroy, while some are neutralizing antibodies. [2]

For COVID-19, it is postulated that neutralizing antibodies play an important role. Common mechanisms may involve one or more of the following: 1) aggregate viruses preventing binding and entry; 2) bind to the viral attachment protein or the cellular receptor and prevent entry; 3) prevent conformational changes necessary for fusion; 4) destabilize the virus and cause release of viral nucleic acid outside the cell; 5) prevent uncoating of the virus capsid; or 6) prevent the release of progeny virus from infected cells.[1,3,4]

Its use in symptomatic patients likely "blunts" virus replication while waiting for the host's immune system to be able to mount a response to the virus.[1]

It is generally agreed that the immunomodulatory mechanism of action can be extrapolated from that of IVIG. Encouraging results from the different case series and reports from China (Appendix B) seem to be consistent with some anti-inflammatory effects.

Clinical Studies

In this present epidemic caused by SARS-CoV-2, there are 2 completed case series on the use of convalescent plasma. In a pilot study by Duan et al, each patient with severe COVID-19 received one dose (200 ml) of convalescent plasma with neutralizing antibody titers at or exceeding a 1:640 dilution between day 11 to day 20 from onset of symptoms. All 10 adult patients had improvement in symptoms (e.g. fever, cough, shortness of breath and chest pain) within 3 days of transfusion and demonstrated radiological improvement in pulmonary lesions. The study revealed that CP could significantly increase or maintain the neutralizing antibodies at high level leading to disappearance of viremia in 7 days.[5]

In another case series by Sheng et al, 5 critically ill adult patients in China were given two consecutive doses of 200 to 250 ml convalescent plasma (SARS -CoV-2 IgG titers >1000 and & neutralizing antibody titer >40) 1 day apart. These were given between day 10 to day 22, and improvement in clinical status was seen, as evidenced by weaning off mechanical ventilation, reduction in viral load, improvement in oxygenation and clinical stabilization of symptoms. All showed that viral load decreased and became negative within 12 days post transfusion. Transfusion of convalescent plasma in both studies resulted in no serious adverse effects in all recipients.[6]

Other interventional trials in several countries are currently being conducted. (Appendix B)

Recommended Dose

The appropriate volume for transfusion has not yet been determined. Based on previous pandemics and expert opinion, a volume from 200 to 600 ml (to 8 to 10 ml/kg, with a maximum of 600 ml) once per day and up to three consecutive days has been suggested.[7,8,9]

Improvement of clinical signs & symptoms and decrease in values of clinical markers of inflammation were seen when plasma transfusion was started anywhere from day 10- day 22.[5,6]

A more restricted recommendation comes from the Italian Society of Transfusion Medicine and Immunohematology (SIMTI) and Italian Society of Hemapheresis and cell Manipulation (SidEM), that states that the optimal period to give immune plasma transfusion is within 7 days from the onset of symptoms as this coincides with peak of viremia within first week.[7] At the same time, there is evidence that giving it within the first 2 weeks may still be beneficial. Administration of immune plasma beyond 3 weeks from the onset of the disease seem to render it ineffective.[8]

Adverse Effects

There can be mild reactions like evanescent red spots as reported by Duan et al.[5] Other non-infectious hazards of tranfusions are allergic transfusion reactions and transfusion associated circulatory overload (TACO).[7] The risk for these adverse effects are likely to be no different from those of standard plasm transfusion. However, it may carry some risk of tranfusion related acute lung injury (TRALI)[10] considering its use in active treatment of individuals with pulmonary disease. The specific risk of transfusion-transmitted SARS COV2 is highly unlikely if one considers that only 1% of symptomatic patients have been reported to have detectable SARS-CoV-2 RNA in their blood and only asymptomatic plasma donors are recruited. Since there is yet no proof of COVID-19 infection via blood transfusion, its significance is largely theoretical.

There is a theoretical possibility of antibody-dependent enhancement (ADE) following transfusion of human anti-SARS-CoV-2 plasma.[11] ADE refers to a process

whereby there is enhancement of disease in the presence of antibodies to a different strain of the virus causing the disease. As there is more than one strain of SARS-CoV-2 that have been identified, occurrence of this phenomenon has been offered as a possible reason for the geographic variation in disease severity

Conclusion:

Use of convalescent plasma in COVID-19 early in the disease process or for prophylaxis is a potentially safe and effective treatment. However, even in a pandemic, when it could be utilized as the most direct and simplest antibody treatment, a risk benefit assessment must be carried out when used in critically ill patients with significant pulmonary disease. Its efficacy may also be affected by the variability of the levels of neutralizing antibodies present in a particular donor plasma. Well controlled clinical trials are still needed to confirm its efficacy and safety for different application in COVID-19.

REFERENCES:

1. Burton DR. Antibodies, viruses and vaccines. Nat Rev Immunol. 2002; 2:706–713.
2. Janeway CA, Travers Paul, Walport Mark, Shlomchik Mark, editors. Immunobiology. Fifth ed. New York: Garland Publishing; 2001.
3. Marasco WA, Sui J. The growth and potential of human antiviral monoclonal antibody therapeutics. Nat Biotechnol. 2007; 25:1421–1434.
4. Reading SA, Dimmock NJ. Neutralization of animal virus infectivity by antibody. Arch Virol. 2007; 152:1047–1059.
5. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of National Academy of Sciences of the United States of America. Available from: https://www.pnas.org/content/early/2020/04/02/2004168117).
6. Shen C, Wang Z, Zhao F, et al.Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020. doi: 10.1001/jama.2020.4783. [Epub ahead of print].
7. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020. pii: 138745. doi: 10.1172/JCI138745. [Epub ahead of print].
8. Accorsi P, Berti P, de Angelis V, et al. “Position paper” on the preparation of immune plasma to be used in the treatment of patients with COVID-19. 26.03.2020. Available from: https://isbtweb.org/fileadmin/user_upload/Italy.pdf.
9. US Food and Drug Administration. Recommendations for investigational COVID-19 convalescent plasma. Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed on: 30 March 2020.
10. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med. 2007; 176(9):886–891. doi.org/10.1164/rccm.200702-271OC.
11. Wan Y, Shang J, Sun S, et al. Molecular mechanism for anti- body-dependent enhancement of coronavirus entry. J Virol. 2020; 94(5):e02015-19. doi: 10.1128/JVI.02015-19.

3. HYPERIMMUNE GLOBULIN

Introduction

Hyperimmune globulin is collected from convalescent plasma donors with higher titers of the antibody of interest as determined by a particular standard. High titers can be achieved by natural immunity, prophylactic immunization or target immunization. Based on the procedure for production of SARS-CoV hyperimmune globulin,[1] convalescent plasma samples from different individuals were pooled to undergo cold ethanol precipitation. The separated serum portion of the blood underwent ion-exchange chromatography followed by virus inactivation and removal procedures to ensure safety. Optimal titers of neutralizing antibodies were then achieved. For COVID-19, the levels suitable for active treatment and prevention have yet to determined.

Mechanism of Action

The effects of hyperimmune globulin is based on the same principle of action of neutralizing antibodies as mentioned in CP. With the higher titers of purified neutralizing antibodies, it is expected to be more efficient than CP in clearing the virus.

Clinical Studies

There are no studies at present due to product unavailability.

Recommended Dose

No recommended dose as of this time.

Adverse Effects

Since the product is presently still unavailable, adverse reactions are largely unknown. They may, however, be very similar to the adverse reactions of convalescent plasma preparations if given intravenously.

Availability

Two pharmaceutical companies are eyeing its development:

Takeda Pharmaceutical Company Limited (TSE:4502/NYSE: TAK) announced early in March the company's plan to develop a plasma-derived therapy for anti-Severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) polyclonal hyperimmune globulin (H-IG), TAK-888, to treat high-risk individuals with COVID-19.[2]

Emergent BioSolutions (NYSE:EBS) is also developing plasma-based treatments for COVID-19, including COVID-HIG, which will be derived from recovered patients, and COVID-EIG, made from plasma taken from horses that were given the virus.[3]

Conclusion

Hyperimmune globulin has potential for a more efficient cost/benefit approach to preventive therapy for COVID-19. Its efficacy for prophylaxis as well as active treatment must be proven by better controlled trials once the product becomes available.

REFERENCES:

1) Zhang Z, Xie YW, Hong J, et al. Purification of severe acute respiratory syndrome hyperimmune globulins for intravenous injection from convalescent plasma. Transfusion. 2005; 45(7):1160-4.
2) Hopkins JS. Drugmaker Takeda is working on coronavirus drug. Wall Street Journal. Published March 4, 2020. Available from: https://www.wsj.com/articles/drugmaker-takeda-is-working-on-coronavirus-drug-11583301660. Accessed March 10, 2020.
3) Emergent BioSolutions. Emergent BioSolutions Partners with U.S. Government for Comprehensive Response to Expedite Development of Plasma-Derived Therapy for COVID-19. GlobeNewswire. Published April 02, 2020. Available from: https://www.globenewswire.com/news-release/2020/04/02/2011095/0/en/Emergent-BioSolutions-Partners-with-U-S-Government-for-Comprehensive-Response-to-Expedite-Development-of-Plasma-Derived-Therapy-for-COVID-19.html.

NON- PATHOGEN-SPECIFIC IMMUNOMODULATORS

1. CORTICOSTEROIDS

Introduction

Corticosteroids are anti-inflammatory medications which have been used as an alternative therapy for cytokine storm syndrome (CSS).

Given a patient with a potentially lethal state of hyperinflammation, it may seem that immunosuppression with corticosteroids may be beneficial. Such was the rationale for the use of steroids in the SARS-CoV outbreak in 2003 as well as for MERS-CoV in 2018.[1,2,3]

Mechanism of Action

Its mechanism of action is the inhibition of the transcription of many cytokine genes including IL-1, IL-6 and TNF. These inflammatory mediators are integral in the cascade of cytokine storm syndrome which has been observed in some fatal cases of COVID-19 infections. Corticosteroids suppress hyperinflammation and eliminate activated immune cells and infected antigen presenting cells (APCs), cytotoxic lymphocytes (CTLs) and histiocytes. Through its mechanism of action it is regarded as a standard therapy in addressing CSS as well as in the treatment of Macrophage Activation Syndrome (MAS) secondary to rheumatic diseases.[4,5] However, its role in viral infections particularly, COVID-19 remains obscure.

Clinical Studies

As of April 20, 2020, there is no published evidence from randomized controlled trials to support the use of glucocorticosteroids for COVID-19.[2]

According to the WHO Interim Guidance dated March 13, 2020, systemic glucocorticoids should not be given routinely to treat viral pneumonia outside of clinical trials. This is due to the lack of evidence of effectiveness and possible harm.[6] The recommendation is based on previous studies on SARS where corticosteroids administered to patients with SARS provided no survival benefit and may pose possible harm. A conditional recommendation may be made, though, for patients with concomitant asthma exacerbation or COPD or sepsis.[6] Another study where steroids were used for MERS-CoV patients found that it had no effect on mortality but delayed lower respiratory tract clearance of MERS-CoV.[7] Some studies have shown a small improvement in mortality and faster resolution of shock with steroid use.[8]

Researchers in King's College London found that low doses of prednisolone or tacrolimus could be helpful in the treatment of COVID-19, however, further investigation is needed.[9] In another article, corticosteroids may be judiciously used in patients with established pulmonary disease and hypoxia who progress to require mechanical ventilation.[10]

One published retrospective observational study done in Wuhan Union Hospital looked at the effect of giving IV methylprednisolone 1-2mg/kg per day to patients with severe COVID-19 pneumonia. Out of 46 patients, 26 received methylprednisolone in addition to standard of care. These patients had shorter duration of fever, faster improvement of SpO2 and better resolution of chest CT scan findings.[11]

In another observational study in First Hospital in Changsha, 10 COVID-19 patients were given low dose methylprednisolone plus 10 grams/day of IVIG aside from standard of care. Despite that, all 10 patients were persistently febrile, had decreasing PaO2/FiO2, decreasing lymphocyte counts and progression of chest CT scan findings. Methylprednisolone was increased to 160 mg/day, IV Ig was also increased to 20 grams/day. Clinical improvement was noted thereafter, PaO2/FiO2 and lymphocyte counts increased and infiltrates in the chest CT scan decreased. [12]

Though promising, results of these studies must be interpreted with caution as there are methodological issues and the sample size is small.

As of April 20, 2020, there are 2 completed observational studies (discussed above),[11, 12] 1 randomized controlled trial still for publication and seven (7)) randomized controlled trials and 1 interventional non-randomized trial on the use of steroids for COVID-19 are still ongoing. (Appendix C)

Recommended Dose

The use of methylprednisolone at 1-2 mg/kg/day for 5 to 7 days has been proposed.[2]

Adverse Effects

Clinicians who will consider using corticosteroids for COVID-19 and sepsis must evaluate the benefit of the slight reduction in mortality versus the risk of prolonged viral shedding. Patients must be closely monitored and issues on hyperglycemia and electrolyte imbalances should be addressed. One must also watch out for recurrence of inflammation, secondary infections and adrenal insufficiency.

Conclusion

Corticosteroids are not routinely recommended for COVID-19. Its judicious use may be employed early on in the disease, when circumstances merit its use. It may also be an option for concomitant conditions such as asthma, COPD or sepsis/septic shock refractory to vasopressors and fluids. The risk particularly on the delayed viral clearance and concomitant infection versus the benefit of its anti-inflammatory effect must always be weighed when carefully considering this for use in patients with severe COVID-19.

REFERENCES:

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb; 395(10223):497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020 March; 214:108393. doi: 10.1016/j.clim.2020.108393. [Epub ahead of print]
3. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence. Ecancermedicalscience. 2020 Mar 27; 14:1022. doi: 10.3332/ecancer.2020.1022. eCollection 2020
4. Favallia EG, Ingegnolia F, De Luciaa O, Cincinellib G. COVID-19 infection and rheumatoid arthritis: faraways, so close. Autoimmunity Reviews. 2020; 19: 102523. doi.org/10.1016/j.autrev.2020.102523
5. Ozen S, Esenboga S. Alternative therapies for cytokine storm syndrome. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. pp. 581-583.
6. World Health Organization Interim Guidance. Clinical management of severe acute respiratory infection when COVID-19 is suspected. WHO Reference Number WHO/2019-nCoV/Clinical/2020.4
7. BC Centre for Disease Control. Unproven Therapies for COVID-19. Updated April 12, 2020. Available from: http://www.bccdc.ca/Health-Professionals-Site/Documents/Guidelines_Unproven_Therapies_COVID-19.pdf. Accessed on: 20 April 2020
8. Doctors Try Steroids to Treat Coronavirus Patients, Against WHO Counsel. Available from: https://www.wsj.com/articles/doctors-try-steroids-to-treat-coronavirus-patients-against-who-counsel-11584878400. Accessed on: 20 April 2020
9. New study identifies drugs that are safe to use in COVID-19 treatment. Available from: https://www.pmlive.com/pharma_news/new_study_identifies_drugs_that_are_safe_to_use_in_covid-19_treatment_1332732?SQ_DESIGN_NAME=2&. Accessed on: 20 April 2020
10. Siddiqi HK, Mehra MR. COVID-19 Illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant, 2020 Mar 20 [Epub ahead of print]
11. Wang Y, Jiang W, He Q, et al. Early, low-dose, short term application of corticosteroid treatment in patients with severe covid 19 pneumonia: A single center experience from Wuhan China. Available from: https://www.researchgate.net/publication/339892221_Early_low-dose_and_short-term_application_of_corticosteroid_treatment_in_patients_with_severe_COVID-19_pneumonia_single-center_experience_from_Wuhan_China. (preprint). Accessed on: 20 April 2020
12. Zhou Z, Xie S, Zhang J, et al. Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses COVID-19 patients who have failed low-dose therapy. *Preprints.* 2020. 2020030065 (doi: 10.20944/preprints202003.0065.v1). Accessed on 21 April 2020.

2. HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (CQ)

Introduction

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are well-known drugs for its effectiveness in treating malaria and autoimmune diseases. The hydroxyethyl group of HCQ makes it more soluble, less toxic, with lesser side effects and hence safer than CQ.[1]

Mechanism of Action

HCQ and CQ inhibit viral entry by inhibition of synthesis of sialic acid and by disruption of protein glycosylation interfering viral attachment and entry.[2,3] They interfere with viral release into host cell by increasing endosomal pH, blocking the proteases responsible for coronavirus/endosomal fusion that release virus into cell.[2,4] HCQ reduces viral infectivity by inhibiting protein glycosylation and maturation of viral protein.[2,5] HCQ's immune modulation is demonstrated by reduction of toll-like receptors and cyclic GMAP synthase-stimulator of interferon genes (cGAS-STING) signaling which reduce the release of proinflammatory cytokines [2,6]

Clinical Studies

Efficacy of HCQ or CQ Monotherapy for COVID-19

As of April 20, 2020, there are 2 randomized controlled trials and 1 observational study completed on the efficacy and safety of hydroxychloroquine for COVID-19. Improvement in CT scan findings were observed among those who received standard of care and hydroxychloroquine compared to those who received standard of care alone.[7,8] No significant differences with the time of normalization of temperature were detected nor with the reduction of admissions to ICU or deaths in the two treatment groups. [7,8,9] There were differences however in the standard of care used for the 3 studies. Use of co-therapies (immunoglobulin, corticosteroids and other antimicrobials) was the standard of care for the study of Chen Z.[7]

Efficacy of Hydroxychloroquine and Azithromycin for COVID-19

There is only one open-label clinical trial[10] and 2 observational studies[11,12] on the use of hydroxychloroquine and azithromycin for patients with COVID-19. The use of the combination therapy was associated with a reduction in the viral load, however result of the study should be interpreted with caution due to the methodologic concerns and small sample size.[10]

The Philippine Society for Microbiology and Infectious Diseases (PSMID) has included in their interim guideline HCQ as one of the medications to be considered for use in hospitalized, probable or confirmed COVID-19 cases with moderate to severe pneumonia.[13]

Several national and society guidelines (China, Italy, Netherlands, Belgium) have included HCQ in the management of COVID-19 pneumonia.[14,15,16]

There are ongoing clinical trials on the use of HCQ or CQ as monotherapy or in combinations with other drugs for patients with COVID-19. (Appendix D)

Recommended Dose

Pediatric Dosing:[17]

HCQ (200 mg tablet) 5 mg/kg/day BID(Max 400 mg).
Day 1: 6-8 y/o 1 tab BID; 9–11y/o 1½ Tab BID; ≥12 y/o 2 Tabs BID.
Day 2 -5: 6-8 y/o ½ tab BID; 9-11 y/o ½ up to 1 Tab BID; >12 y/o 1 tab bid.
Should not be given to < 6 years old.

CQ 10 mg (base)/kg/day BID (Max 500 mg phosphate or 300 mg base/dose):
0-11 months ½ tab BID; 1-3 y/o 1 tab BID; 4-6 y/o 1 ½ tab BID; 7-11 y/o 2 tabs BID; 12-15 y/o3 tabs BID; ≥16 y/o 4 tabs BID

These drugs should be given for a total treatment duration of 5-10 days.

Adult:[13]

HCQ: 200mg tab 2 tabs BID day 1 then 1 tab BID x 9 days

CQ: 500 mg BID x 10 days

Adverse Effects

The use of HCQ or QC in patients with COVID-19 has been associated with QTc prolongation and torsades de pointes.[9, 18] The development of acute renal failure among those given the combination of HCQ and azithromycin was a strong predictor of severe QTc prolongation.[18] Use of HCQ should be avoided or used with caution and partnered with close monitoring in those with prolonged baseline QTc interval or on other agents that affect cardiac conduction. Other adverse effects reported among patients with COVID-19 given HCQ were rash, diarrhea, nausea, vomiting and increase in aspartate aminotransferase.[7,8,10,11]

Conclusion

There is no high-quality evidence on the efficacy of HCQ and CQ either as monotherapy or in combination with other drugs for COVID-19. The use of these drugs during the COVID-19 pandemic as interim management while awaiting results of the clinical trials should be weighed versus the risks associated with them.

REFERENCES:

1. Zhou D, Dai SM, Tong Q (2020 March 2020) COVID-19: a recommendation to examine the effect of hydroxychloroquine in prevention infection and progression. Journal of Antimicromicrobial chemotherapy. dkaa114, https://doi.org/10.1093/jac/dkaa114 Retrieved april 10, 2020
2. Devaux, C.A., Rolain, J.M., Colson, P. and Raoult, D., 2020. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. International Journal of Antimicrobial Agents, p.105938.
3. Vincent MJ, Bergeron E, Benjannet S et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005; 2: 69. Google Scholar Crossref PubMed
4. Yang ZY, et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced dentritic cell transfer through DC-SIGN.J Virol.2004 Jun: 78 (11); 5642-50.
5. Savarino, A., Mothanje,B, Rastrelli, E ,et al. Anti HIV effects of chloroquine: inhibition of viral article glycosylation and synergism with protease inhibitors. Journal of Acquired Immune Deficiency Syndromes. 35(3):223-232, March 1, 2004
6. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. March 21, 2020. Nature Reviews Rheumatology 16(3): 1-12 February 2020. Doi:10.1038/241584-020-0372-x. Retrieved April 10, 2020
7. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv Prepr Serv Health Sci. 2020. doi:doi: https://doi.org/10.1101/2020.03.22.20040758
8. Chen J, Lui D, Lui L et al. (2020) A Pilot study of hydroxychloroquine in the treatment of patients with coronavirus disease 19 (COVID 19). Journal of Zhejiang University http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03
9. Mahévas M, Tran V, Roumier M, Chabrol A, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. 10.1101/2020.04.10.20060699.
10. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. March 2020:105949. doi: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: an observational study. 2020. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/ COVID-IHU-2-1.pdf
12. Molina JM, Delaugerre C, Goff JL, 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. Médecine Mal Infect. March 2020. doi:10.1016/j.medmal.2020.03.006
13. Philippine Society for Microbiology and Infectious Diseases. Interim guidelines in the management of adult patients with suspected or confirmed COVID-19 Infections. Version 2.1 as of 31 March 2020
14. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). China National Health Commission, 2020.
15. Italian Society of Infectious and Tropical Diseases. Guideline for the treatment of people with COVID-19 disease. 2020
16. Interim clinical guidelines for patients suspected of/confirmed with COVID-19 infection. https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf

17. Pediatric Infectious Disease Society of the Philippines. Interim guidelines on the screening, assessment and clinical management of pediatric patients with suspected or confirmed coronavirus disease 2019 (COVID-19) Version 2, 12 April 2020
18. Chorin E, Matthew D, Shulman E, Wadhwani L, Kohen R, Barbhiya C. The QT Interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin.

3. AZITHROMYCIN

Introduction

Macrolides, like azithromycin, are a class of antimicrobials with activity mainly against gram-positive cocci and atypical pathogens.[1] However, there is an accumulating body of evidence that it has broad activities as immunomodulatory drugs as well.

Mechanism of Action

The mechanism of action of macrolides as immunomodulators reveals several effects dependent on the target cells. In airway epithelial cells, it inhibits chloride secretion, mucus secretion, adhesion molecules, proinflammatory cytokines and inflammatory mediators. It also enhances tight junctions, cell barriers and defensins. It inhibits neutrophil chemotaxis, adhesion molecules, proinflammatory cytokines, elastase, reactive oxygen species while it promotes apoptosis[2] and regulation of immune cells. These changes underlie many immunomodulatory effects of azithromycin, contributing to resolution of acute infections and reduction of exacerbations in chronic airway diseases.[3]

Clinical Studies

Azithromycin alone has no proven antimicrobial activity against COVID-19 but the synergistic effect with hydroxychloroquine can be attributed to its immunomodulatory action. At present, there are 366 registered clinical trials about COVID 19 in the United States National Institute of Health and among these, 24 studies include the use of Azithromycin, either alone or in combination with other treatment modalities.

A study of combination therapy with hydroxychloroquine was published on March 2020. In an open-label study of 36 patients with COVID-19, the use of azithromycin in combination with hydroxychloroquine (n=6) compared to hydroxychloroquine alone (n=14) appeared to be associated with a more rapid decline in viral RNA. At day 6 post-inclusion, all of the patients treated with hydroxychloroquine and azithromycin combination were virologically cured.[4] The results this ongoing study should be interpreted with caution due to methodologic concerns and small sample size.

Adverse Effects

Reactions like QTc prolongation and ventricular arrhythmias, including torsades de pointes have been reported. Patients admitted with COVID-19 are likely to have longer baseline QTc and have higher potential arrhythmic risks especially in the background of a previous cardiac pathology (arrhythmias, heart failure, hypokalemia, hypomagnesemia)[5,6] QTc monitoring in this setting is essential to identify those who are at increased risk for torsades de pointes so aggressive countermeasures may be implemented. [6,7]

Hypersensitivity to azithromycin and other macrolides as well as a history of cholestatic jaundice or hepatic dysfunction are contraindications.

Recommended Dose

Adult: 500 mg once a day for 5 days or 500 mg once on Day 1 then 250 mg once daily on Day 2- 5

Pediatric: 10 mg/kg/day once a day (max of 500 mg/day) for 5 days [7]

Conclusion

Based on this limited data, azithromycin has shown positive results when used in combination with hydroxychloroquine in COVID-19 patients. However, there are no studies on the use of azithromycin alone for COVID-19.

REFERENCES:

1. Giamerellos-Bourboulis, EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators; Elsevier; Int J Antimicrob Agents. 2008 Jan; 31(1): 12-20. Epub 2007 Nov 1
2. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev 2010; 23: 590-615. [Internet]* doi:10.1128/CMR.00078-09
3. Parnham MJ, Haber VE, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: Mechanisms of action and their relevance for clinical applica-tions. Pharmacol Ther [Internet] 2014;143:225–245. doi:10.1016/j.pharmthera.2014.03.003.
4. Gautret P, Lagier JC, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Ag. In press. 2020 Mar 20. https://www.sciencedirect.com/science/article/pii/S0924857920300996.
5. Gahart B, Nazareno A. Ortega M., Gahart's Intravenous Medications 2020, 36th ed., page 154-155.
6. Interim Guidelines on the screening, assessment and clinical management of pediatric patients with suspected or confirmed coronavirus disease 2019 (CoViD-19). Philippine Pediatric Society and Pediatric Infectious Diseases Society of the Philippines. 2020 March 30
7. Simpson T, Kovacs R, Stecker E. Ventricular Arrhythmia Risk Due to Hydroxychloroquin - Azithromycin Treatment For COVID-19, Cardiology Magazine, American College of Cardiology. 2020 Apr

4. TARGETED MONOCLONAL ANTIBODIES (CYTOKINE ANTAGONISTS)

a. INTERLEUKIN 6 (IL-6) INHIBITORS

Introduction

IL-6 and IL-1 are two of the main proinflammatory cytokines released during a viral infection. IL-6 seems to hold a key role in cytokine storm pathophysiology since highly elevated IL-6 levels are seen in patients with cytokine storm.[1] In severe or complicated cases, they were almost three times higher than the non-severe cases.[2,3,4] The use of IL-6 inhibitors in the management of patients with COVID-19 may ameliorate the severe damage to the lung caused by the cytokine release.

Mechanism of Action

The IL-6 inhibitors (tocilizumab, sarilumab and siltuximab) bind to both the membrane-bound and soluble forms of IL-6 receptors thereby blocking the classical and trans signal transduction and its mediated immune response.[5]

Tocilizumab is a recombinant human IL-6 monoclonal antibody that has been approved for rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systematic juvenile idiopathic arthritis. It is already approved by the USFDA for the treatment of cytokine release syndrome (CRS) that is severe or life-threatening. The Philippine FDA considers it as a Drug Under Emergency Use (DEU).[6] The agent is used in adults and children aged 2 years and older who have CRS caused by Chimeric Antigen Receptor (CAR) T-cell therapy.[6]

Siltuximab is a chimeric monoclonal antibody approved for treatment of adults with multicentric Castleman's disease who are human immunodeficiency virus and human herpes virus-8 negative.

Sarilumab is a human IgG1 monoclonal antibody that has been approved by the FDA for rheumatoid arthritis.

Clinical Studies

There are no published clinical trials on the efficacy and safety of IL-6 inhibitors for the management of patients with COVID-19.

There is only one observational study [7], 1 case report [8], and 15 registered clinical trials on the use of tocilizumab for COVID-19 patients. (Appendix F). Tocilizumab was given to 21 patients with severe or critical COVID-19 pneumonia. The body temperature of all patients returned to normal after one day of tocilizumab. Majority of the patients had improvements in their peripheral oxygen saturation, CRP levels and chest CT scans.[7]

A single-center case-control study on the use of siltuximab in adult COVID-19 patients with ARDS is ongoing (NCT04322188). Interim data showed reduced need for ventilation for most of the included patients.[9]

At present, there are no data from clinical trials on the efficacy of sarilumab for patients with COVID-19. There are 5 registered studies in clinicaltrials.gov on the efficacy of sarilumab in adult patients hospitalized with severe COVID-19 pneumonia.

The Chinese Clinical Guidance for COVID-19 [10] and the Italian Society of Infectious Diseases and Tropical Diseases COVID-19 Guideline[11] have recommended the use of tocilizumab as a treatment option for patients with severe COVID-19.

Recommended Dose

Tocilizumab:

Adult: 8 mg/kg (maximum: 800 mg/dose) as a single dose; may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve[12]
4-8 mg/kg single dose or 400mg IV diluted in 0.9 NS to 100 ml, given as 2-hour infusion; a single extra dose may be given after 12 hours at the discretion of the provider[13]

Pediatric : 8 mg/kg/dose IV once; an additional dose may be given 12 hours after the first if clinical symptoms worsen or show no improvement. maximum dose: 800 mg/dose[14]

Sarilumab: 400 mg single IV dose or 200-400 mg SC dose[15]

Siltuximab: 11mg/kg infused over one hour with a potential second dose at the physician's discretion[9]

Adverse Effects

In the observational study for COVID-19 patients, there have been no reports of subsequent pulmonary infection, deterioration of illness nor death among those given tocilizumab. There were likewise no adverse drug reactions reported.[7]

Tocilizumab was associated with an increased risk of infectious respiratory adverse events in patients with rheumatoid arthritis.[16] Both tocilizumab and sarilumab carry FDA black box warnings of serious infections, such as tuberculosis and invasive fungal infections, leading to hospitalization or death.

Conclusion

There is limited evidence to evaluate the efficacy and safety of the IL-6 inhibitors (tocilizumab and siltuximab) on patients with COVID-19. There are no completed clinical trials for Sarilumab at present. Although benefit was seen in one observational study on

tocilizumab for severe COVID-19, more data from ongoing and planned clinical trials are needed to establish the role of IL-6 inhibitors in the management of such patients.

REFERENCES:

1. Shimabukuro-Vornhagen A. Reference: Shimabukuro-Vornhagen A, Godel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018; 6:56. https://dx.doi.org/10.1186%2Fs40425-018-0343-9
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506.
3. Zhou F, Yu T, Du R, Fan G, Liu G, Liu Z, et al.. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. Lancet. 2020 Mar 28;395(10229):1054-1062.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. *Clinical Infectious Diseases*. 2020 March.
5. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce in the mortality [published online ahead of print, 2020 Mar 28]. *Int J Antimicrob Agents*. 2020;105954.
6. Philippine FDA Circular No. 2020-12. Guidelines for the registration of drug products under emergency use (DEU) for the COVID-19.
7. Le R, Li L, Yuan W, Shord S, Nie L, Habtemariam BA, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncol. 23 (2018); 943–947.
8. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv. March 2020. http://chinaxiv.org/abs/202003.00026.
9. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Advances*. doi:10.1182/bloodadvances.2020001907.
10. Gritti G, Raimondi F, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. MedRxiv April 2010 (preprint). Accessed April 6, 2020. doi.org/10.1101/2020.04.01.20048561.
11. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). China National Health Commission, 2020.
12. Italian Society of Infectious and Tropical Diseases. Guideline for the treatment of people with COVID-19 disease. 2020
13. Genentech Inc. Actemra use in coronavirus disease 2019 (COVID-19) [press release]. South San Francisco, CA: Genentech, a member of the Roche Group
14. Philippine Society for Microbiology and Infectious Diseases Interim Guidelines in the Management of Adult Patients with Suspected or Confirmed COVID-19 Infections.Version 2.1 as of 31 March 2020
15. National Institutes of Health (NIH). Tocilizumab in COVID-19 pneumonia. Updated March 20, 2020. https://www.clinicaltrials.gov/ct2/show/NCT043170921
16. National Institutes of Health (NIH). Tocilizumab in COVID-19 pneumonia. Updated April 6, 2020. https://www.clinicaltrials.gov/ct2/show/NCT04315298
17. Geng Z, Yu Y, Hu S, et al. Tocilizumab and the risk of respiratory adverse events in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomised controlled trials. Clinical and experimental rheumatology. 2019;37(2):318-23.

4. TARGETED MONOCLONAL ANTIBODIES (CYTOKINE ANTAGONISTS)

b. INTERLEUKIN 1 (IL-1) INHIBITORS

Introduction

Interleukin-1 (IL-1) is a pro-inflammatory cytokine released by cells of the innate immune system after exposure to pathogenic organisms whether viral, fungal or bacterial.[1] IL-1β is one of 2 ligands of IL-1 and is one of the most powerful proinflammatory cytokines; though it has protective actions against infections, it is also capable of inducing several detrimental biologic processes such as apoptosis, pyroptosis and cell proliferation which can cause tissue damage and organ dysfunction in the host. Its pro-inflammatory activity is regulated by inflammasomes which inhibits IL-1 transcription and processing intracellularly and thus further hyperinflammatory states.[2,3]

Mechanism of Action

IL-1 antagonists work by capturing IL-1β and hindering it from binding to the IL-1 receptor, hence preventing the pro-inflammatory cascade. Due to their IL-1 antagonistic effects these can interfere with the immune response.

1. Anakinra is the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1RA) which prevents the binding of IL-1α as well as IL-1β to IL-1R1. It has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with active rheumatoid arthritis (RA). In RA, studies have indicated that anakinra has a favorable risk–benefit profile. It has a relatively short half-life of 4 to 6 hours; compliance was reported to be high even with daily subcutaneous injection regimen.[4]
2. Rilonacept is a recombinant humanized monoclonal antibody that has a high affinity for IL-1 and potently inhibits its activity. It is administered subcutaneously beginning with a loading dose followed by a weekly injection of half the loading dose. They are indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome in adults and children aged 12 years and older.[5]
3. Canakinumab is a specific human monoclonal IgG1 antibody targeted against IL-1 β. It is also indicated for the treatment of CAPS.[6]

IL-1 And COVID-19

IL-1 has been noted to be over-expressed in SARS-CoV. In COVID-19 disease, the virus binds to toll-like receptors (TLRs) which activate the IL-1 inflammasomes producing more IL-1β in a dysregulated manner. IL-1β facilitates the hyperinflammatory reaction in the lungs, fever and fibrosis causing respiratory complications in the host.[7]

Clinical Studies

There are no studies on the use of interleukin-1 receptor antagonists (IL-1RA) against COVID-19 and even against SARS and MERS-CoV. Since COVID-19 can present with hyper-inflammation, the use of an interleukin-1 receptor antagonist, anakinra, has been proposed. This is based on a re-analysis of data from a confirmatory Phase III trial, which was a prospective, randomized, double-blind, placebo-controlled, multicenter study. It looked at therapeutic efficacy and safety of an IL-1RA as an adjunctive treatment in patients with severe sepsis. It was given as 100 mg IV bolus and followed by a 72-hr continuous intravenous infusion at 2.0 mg/kg/hr. This study was terminated after the second interim analysis failed to show a statistically significant decrease in mortality.[8] A re-analysis of the study data, done 19 years later, looked at the efficacy of anakinra (recombinant IL-1RA) in improving 28-day survival in sepsis patients with features of macrophage activation syndrome (MAS). Using multiple regression analysis, it was shown that among patients on anakinra the adjusted odds of 28-day mortality is 87% lower than those on placebo [OR for death 0.13 (0.03–0.71), p = 0.018], after controlling for covariates (age, AKI, ARDS).[9]

Some patients with COVID-19 progress to a third stage with cytokine storm syndrome/MAS. Based on the above study, there are currently three clinical trials registered in ClinicalTrials.gov using anakinra alone or in combination with other immunomodulators (see Appendix G)

Recommended Dose

There is currently no recommended dose for anakinra for COVID-19. The doses and route of administration in the clinical trials vary.

Adverse Effects

The most frequently reported adverse events were injection-site reactions.[5] An increased frequency of infections has been reported with anakinra use similar to other biologic agents. Opportunistic infections, though, are rare in anakinra-users. Due to its short half-life and duration of activity, it is considered to be safer than other biologic agents even if given for long term use (10 years).[1]

Conclusion

Studies for IL-1 receptor antagonists are limited to anakinra. The use of anakinra to prolong survival in cytokine storm syndrome (CSS) is based on indirect evidence; hence, its use for COVID-19 CSS should be in the context of a clinical research.

REFERENCES:

1. Cavalli G and Dinarello CA. Anakinra therapy for non-cancer inflammatory diseases. Front Pharmacol 2018; 9:1157. doi: 10.3389/fphar.2018.01157.
2. Sahoo M, Ceballos-Olvera I, Del barrio L , Re F. Role of the inflammasome, IL-1β and IL-18 in bacterial infections. Scientific World Journal 2011; 11:2037-2050. doi: 10.1100/2011/212680.
3. Shrivastava G, Leon-Jaurez M, Garcia-Cordero J, et al. Inflammasomes and its importance in viral infections. Immunol Res 2016; 64:1101-1117. doi: 10.1007/s12026-016-8873-z.
4. Cohen SB, Rubbert A. Bringing the clinical experience with anakinra to the patient. Rheumatology 2003; 42(Suppl. 2): ii36–ii40. doi:10.1093/rheumatology/keg331.
5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125249lbl.pdf. Accessed 5 April 2020.
6. https://www.pdr.net/drug-summary/Ilaris-canakinumab-434.8451. Accessed 5 April 2020.
7. Russell B, Moss C, Gincy G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence. E-cancer medical science 2020; 14:1022. doi: 10.3332/ecancer.2020.1022.
8. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med. 1997; 25(7):1115–24.
9. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. Crit Care Med 2016; 44: 275–81.

4. TARGETED MONOCLONAL ANTIBODIES (CYTOKINE ANTAGONISTS)

c. TUMOR NECROSIS FACTOR (TNF) INHIBITORS

Introduction

TNF-α plays a role in facilitating the entry of the SARS-CoV into the host cell; thus, anti-TNF-α has been considered as a possible early treatment modality to reduce SARS-CoV infection, as currently being studied in a randomized controlled trial (RCT) in China.

Mechanism of Action

Decrease of angiotensin converting enzyme 2 (ACE2) expression and an increase in the activity of the renin-angiotensin system facilitate entry of the SARS-CoV into the host cell. The SARS-CoV viral protein promotes shedding of the ACE2 ectodomain through the action of TNFα - dependent converting enzyme. This may also be one of the mechanisms of viral infection in SARS-CoV-2. Inhibition of TNFα may then be an important step in reducing SARS-CoV infection and the concomitant target organ damage.[1]

Adalimumab is a human recombinant mAb directed against the soluble and cell-bound forms of tumor necrosis factor alpha (TNF- α).[2]

Clinical Studies

An RCT in the Chinese Clinical Trial Registry (ChiCTR2000030089) presently evaluates adalimumab, an anti-TNF- α receptor antagonist with conventional treatment versus conventional treatment alone in severe and critical COVID-19 infection. They are not yet recruiting at the time of this writing.[3] (Appendix H).

Adverse Effects

Serious adverse reactions (>0.2events/100 patient years) among adults include cellulitis, pneumonia, appendicitis, herpes zoster and urinary tract infection. Less than 0.2/100PY presented with active tuberculosis infection.[4] In children common adverse reactions include infections such as upper respiratory tract infection, nasopharyngitis and headache. Pneumonia was identified as the most common serious adverse reaction.[5]

While TNF inhibitors may interfere with viral penetration into the cell, a slight increase in the risk of viral infection is also possible.[1]

Interactions between Adalimumab and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with methotrexate or commonly used DMARDs (sulfasalazine, hydroxychloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.[6]

Recommended Dose

Studies pertaining to the use of TNF inhibitors are very limited, and there has been no mention of its dose nor timing of administration as of this writing.

Conclusion

Studies on the use of TNF inhibitors in COVID-19 are very limited. A clinical trial has been registered in China, but is not yet recruiting at the time of this writing.

REFERENCES:

1. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! [published online ahead of print, 2020 Mar 20]. Autoimmun Rev. 2020;102523. doi:10.1016/j.autrev.2020.102523
2. Steihm's Immune Deficiencies 2014 https://www.sciencedirect.com/science/article/pii/B9780124055469000492
3. Xu H and Zhou L. A randomized, open-label, controlled trial for the efficacy and safety of Adalimumab Injection in the treatment of patients with severe novel coronavirus pneumonia (COVID-19). Chinese Clinical Trial Registry (ChiCTR2000030089). http://www.chictr.org.cn/showprojen.aspx?proj=49889
4. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013;72(4):517–524. doi:10.1136/annrheumdis-2011-201244
5. Horneff G, Seyger MMB, Arikan D, et al. Safety of Adalimumab in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease. J Pediatr. 2018;201:166–175.e3. doi:10.1016/j.jpeds.2018.05.042
6. Website: https://www.mims.com/philippines/drug/info/humira/drug-interactions

4. TARGETED MONOCLONAL ANTIBODIES (CYTOKINE ANTAGONISTS)

d. INTERFERON

Introduction

Interferons (IFN) are a group of signaling proteins that are produced by host cells early in a viral infection by "interfering" with viral replication and subsequently protect the host cell from viral infections.

Mechanism of Action

Three types of IFNs, types I (IFN-α and IFN-β), II (IFN-γ) and III (IFN-λ), have been classified based on of their genetic, structural, and functional characteristics and their cell-surface receptors.[1] IFN-α was produced principally by leukocytes, IFN-β by epithelial cells, fibroblasts and neurons, and IFN-γ by immune cells. IFN-β, however, undergoes switching to become IFN-α during the amplification phase of the immune response.

As part of the host's antiviral innate immune response, type I IFNs stimulate adjacent cells to produce antiviral proteins, inhibit cell proliferation, regulate apoptosis and promote immunomodulation. Such mechanisms decrease the rate of virus multiplication and also facilitate the adaptive immune response.[2]

Type I IFNs (IFN-α/β) signal through a receptor complex and triggers a pro-inflammatory response via the recruitment and activation of immune cells against viral infections. However, this inflammatory reaction can have serious systemic side effects since the IFN receptor is also expressed on all cells. In contrast, type III IFNs (IFN-λ1-4) signal through a distinct receptor complex, restricted only to epithelial cells and a subset of immune cells, including neutrophils. Therefore, Type III IFN administration as prophylactic treatment in the early stage of COVID-19 would result in an antiviral response localized to epithelial cells, reducing side effects and inflammation.[3] A new long-acting formulation of IFN-α, called pegylated IFN-α, has features that reduces immunogenicity, decreases sensitivity to proteolysis, and lengthens serum half-life.

Studies in animals have shown that SARS-infected cells have low production of interferons. But SARS-CoV remains sensitive to interferons with IFN-β seemingly more potent that IFN-α and IFN-γ.[4] IFN-γ is a pleiotropic cytokine that plays an essential role in multiple phases of immune and inflammatory responses. Although protective in the context of anti-viral host defense, IFN-γ also has been implicated in the pathogenesis of "cytokine storm" and in various autoimmune diseases. Elevated serum interferon gamma has been associated with severe acute respiratory distress in COVID-19.[5] Anti-interferon therapy is approved in the US for the treatment of primary HLH. Emapalumab, a human monoclonal antibody that binds to binds to soluble and receptor-bound forms of IFN-γ is one of investigational drugs for COVID-19.

Clinical Studies

The IFN response is considered important for the control of coronavirus infection. Interferons have their highest utility in the prophylaxis or early post-exposure management of SARS.[2] Currently, an open-label non-randomized controlled trial was launched in China to test the efficacy of IFN-α-2b and Lopinavir/Ritonavir versus routine medical treatment in hospitalized patients with SARS-CoV-2 infections.[6] Moreover, there are at least 10 registered clinical trials examining the efficacy of interferons in the treatment of COVID-19 and 1 open label controlled study investigating the efficacy and safety of intravenous administrations of Emapalumab, an anti-interferon Gamma (Anti-IFNγ) monoclonal antibody, and Anakinra versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 Infection. (Appendix I) These studies are either currently recruiting or not yet recruiting. One study has completed recruitment but there is no available result yet. Therefore, these studies showed that there is no actual proof of the efficacy of IFN treatment yet for COVID-19.

Recommended Dose

IFN-α is suggested to be administered in the early post-exposure treatment of COVID-19: 5 million U or equivalent dose in 2 ml sterile water via vapor inhalation 2x/day for no more than 10 days.[7]

Adverse Effects

Influenza-like symptoms such as fatigue, headache, fever, myalgia, loss of appetite are the most common side effects of IFN treatment, with a severity dependent on the dosage used. These side effects are usually tolerable and tend to become less severe with time. Other side effects include alopecia, weight loss and mental depression which will prompt discontinuation of treatment. Potentially fatal side effects include hepatotoxicity, development of pulmonary infiltrates, pneumonitis, pneumonia and autoimmune diseases.[8]

Interferon reduces the clearance of theophylline and may enhance myelosuppression with other myelosuppressive drugs such as Zidovudine.

Conclusion

Interferons may have a role in early treatment in coronavirus infections, however for COVID-19 evidence is still lacking.

REFERENCES:

1. Li SF, Gong MJ, Zhao FR, et al. Type I interferons: distinct biological activities and current applications for viral infection. Cell Physiol Biochem 2018; 51:2377-2396. doi: 10.1159/000495897. Epub 2018 Dec 11.
2. Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. Cytokine Growth Factor Rev. 2008; 19(2):121-32. doi: 10.1016/j.cytogfr.2008.01.001. Epub 2008 Mar 5.
3. Prokunina-Olsson L, Alphonse N, Dickenson RE, et al. COVID-19 and emerging viral infections: the case for interferon lambda. J Exp Med. 2020; 217(5). pii: e20200653. doi: 10.1084/jem.20200653.
4. Haagmans BL1, Osterhaus AD. Coronaviruses and their therapy. Antiviral Res. 2006; 71(2-3):397-403. Epub 2006 Jun 19.
5. Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. J Clin Invest. 2020. pii: 137647. doi: 10.1172/JCI137647. [Epub ahead of print]
6. Xu Z. Clinical efficacy of novel coronavirus infection treated by combination of interferon regimen and Ritonavir tablets. Chinese Clinical Trial Registry ChiCTR2000031196. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=51112. Accessed on: 19 April 2020.
7. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020; 14(1):58–60. doi:10.5582/ddt.2020.01012.
8. Arnaud P. Different interferons: pharmacology, pharmacokinetics, proposed mechanisms, safety and side effects. Rev Med Interne. 2002; 23 Suppl 4:449s-458s.

5. ANTIVIRALS

Introduction

Antivirals may be viewed by some as anti-infective agents but they do have a role in immunomodulation against all stages of COVID-19. They can be part of medications given starting from the early stage of infection until the later stage of hyper-inflammation and systemic involvement. A study on SARS-CoV suggested, the peak inflammatory cytokine (IL-6 and IL-8) levels concurred with, or after the peak viral load, and preceded or concurred with the maximum pulmonary infiltrates. Thus, it is probable that viral replication leads to the activation of proinflammatory cytokines that, together with other factors, contribute to disease progression.[1]

Antiviral agents have also been included in the World Health Organization's "Solidarity Trial". It is a multi-country clinical trial that seeks to determine the effectiveness of potential treatments. These include: local standard of care, Remdesivir, Chloroquine or Hydroxychloroquine, Lopinavir/Ritonavir, Lopinavir/Ritonavir plus Interferonβ-1α. As of April 20, 2020, over 90 countries are working together in this trial, including the Philippines.[2]

1. LOPINAVIR/RITONAVIR (LPV/r)

Introduction

It is a protease inhibitor used as an antiretroviral treatment in combination with other antiretroviral agents for HIV 1 in adults and pediatric patients [3].

Mechanism of Action

Lopinavir has in vitro inhibitory activity against SARS-CoV. It also blocks a post entry step in the MERS-CoV replication cycle.[3,4] Ritonavir is used in combination with lopinavir to increase the half-life through the inhibition of cytochrome P450[4]. Protease inhibitors prevent cleavage of the viral polyproteins resulting in the formation of non-infectious viral particles.[5] All protease inhibitors increase the release of Macrophage Inflammatory Protein 1α (MIP-1a) and Monocyte Chemotactic Protein-1 (MCP-1) that function to recruit cells of the innate immune system.[6]

Clinical Studies

LPV/r is included in the WHO SOLIDARITY Trial. In a previous trial done in 199 adult patients with severe COVID-19, median time (15 days) to clinical improvement was noted among those treated with LPV/r and this was significantly lesser than the standard treatment group.[7] In a study on 94 patients, COVID-19 mRNA conversion time was correlated with the length of hospital stay among patients treated with LPV/r (with IFN-α) and ribavirin with LPV/r + IFN-α, suggesting its benefit for treatment in mild to moderate COVID 19 patients.[8] A clinical trial for LPV/r as post exposure prophylaxis for 14 days will be done in Canada for ages 18 months and older.[9,10] There are 18 out of

over 20 registered international studies that are currently recruiting to determine the effectiveness of LPV/r in COVID-19 disease. There are no completed studies yet and there are no results published as of April 20, 2020.

Please refer to Appendix J1 to J5 for a list of the clinical studies on antivirals.

Recommended Dose

Adults: 400mg/100 mg twice a day for 10days[11] or 14 days[7].
Pediatric patients: 7-15kg:12mg/3mg/kg; 15-14kg:10mg/2.5mg/kg; >40kg: as adult.[12]

Doses to be taken twice a day for 1–2 weeks.

Adverse Effects

These may include diarrhea, headache, nausea, vomiting, upset stomach, drowsiness, dizziness, bad taste in the mouth and trouble sleeping.

2. RIBAVIRIN/RBV

Introduction

It is a broad-spectrum antiviral drug that hinders viral replication and spread.[13] It is primarily used for Respiratory Syncytial Viral infection, influenza virus and chronic hepatitis C.[1,14] A study on patients with SARS treated with LPV/r and ribavirin had a lower risk of ARDS and death compared with monotherapy[15].

Mechanism of Action

In a review of nucleotide inhibitors, RBV was found to cause nCoV eradication in vitro.[16] For SARS patients, it is effective as prophylaxis and as treatment when combined with IFN-b.[17] Ribavirin has also been found to reduce macrophage activation, diminish Th2 cytokine production and preserve Th1 cytokine production among patients with hepatitis C virus.[18]

Clinical Studies

Ribavirin is presently included in the general treatment of COVID-19 in Chinese treatment guidelines[11] In a study on 94 patients, COVID-19 mRNA conversion time was correlated with the length of hospital stay among patients treated with ribavirin (with LPV/r + IFN-α) andLPV/r + IFN-α, suggesting its benefit for treatment in mild to moderate COVID 19 patients.[8] As of April 20, 2020, there are 4 registered clinical trials, with 2 studies that are currently recruiting, to assess and compare the effectiveness of ribavirin in the treatment of COVID-19 patients. There is one completed study done in Hong Kong that evaluated the safety and efficacy of ribavirin combined with LPV/r and interferon for the treatment of hospitalized COVID 19 patients, however the results are not yet published.

Recommended dose

500 mg intravenous infusion for adults 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir for not more than 10 days.[11]

Adverse Effects

Ribavirin can reduce hemoglobin concentration.[1]It is contraindicated in patients with severe hepatic and renal impairment and in known or suspected pregnant women.[19]

3. ARBIDOL/ UMIFENOVIR

Introduction

This is used for prophylaxis and treatment of influenza A and B viruses and other human pathogenic respiratory viruses. It is only available in China and Russia.[20]

Mechanism of Action

Arbidol has also been reported to produce an immunomodulatory response by inducing interferon production and stimulating the phagocytic function of macrophages.[21] Arbidol prevents the fusion of the viral membrane with the endosome after endocytosis.[20]

Clinical Studies

A cohort study among 111 mild COVID 19 patients showed clinical & radiologic improvement with enhancement of viral clearance among those treated with Arbidol versus empirical treatment.[22] A preliminary report from a case-control study, suggested that it may have the potential to be used as a post-exposure prophylaxis treatment for COVID-19 infections in hospital or family settings but further investigation is needed.[23] As of April 20, 2020, there are a total of 8 registered clinical studies for Arbidol in COVID-19 patients, with 2 studies currently enrolling participants. However, there are no results published yet.

Recommended Dose

200mg by mouth, 3 times a day, for not more than 10 days.[10]

Adverse Effects

Some of the reported side effects are diarrhea, dizziness, and elevated serum transaminase, occasional bradycardia.[20]

4. REMDESIVIR/ RDV/ GS-5734

Introduction

It is an investigational drug with broad-spectrum activities against MERS and SARS in vitro and has been tested for Ebola[14]

Mechanism of Action

It structurally resembles adenosine and can incorporate into nascent RNA, inhibiting RNA-dependent RNA polymerase resulting in premature termination of the RNA chain. This halts the replication of the viral genome[24] and causes a decrease in viral RNA production.[14,25,26] As the SARS-CoV study stated that it is probable that viral replication leads to activation of the pro-inflammatory cytokines, decrease in viral replication may possibly modulate the production of pro-inflammatory cytokines.[1] It potently blocks SARS-CoV-2 infection at low micromolar concentrations and has a high selectivity index.[27]

Clinical Studies

Remdesivir is included in the WHO SOLIDARITY Trial for the treatment of COVID-19. There are 11 registered clinical studies on Remdesivir for the treatment of COVID 19 infection. Ongoing phase III trials are underway to evaluate the efficacy and safety of remdesivir in patients with mild or moderate[28] and severe[29] COVID-19 respiratory disease. There are no completed studies yet as of April 20, 2020.

Recommended Dose

200 mg loading dose on day 1 followed by 100 mg IV once-daily for 4 - 9 days[28,29] Pediatric doses of remdesivir are used in patients with Ebola.[5] There is no data yet for its use in pediatric COVID-19 patients.

Adverse Effects

The safety of remdesivir for COVID-19 patients needs to be assessed by further clinical trials. However in Ebola clinical trials, researches detected increased liver enzyme levels that may or may not indicate liver damage. Researches documented similar increases in liver enzymes in 3 US COVID-19 patients. Typical side effects include nausea and vomiting.[30]

5. FAVIPIRAVIR / T-705/ FAVIPIRA/ FAVILAVIR

Introduction

Favipiravir was approved for treatment of novel influenza on February 15, 2020 in China and is currently undergoing clinical trials in treating COVID-19.[5]

Mechanism of Action

Resembling guanosine, its action is similar to remdesivir. It inhibits the RNA-dependent RNA polymerase of RNA viruses through competitive inhibition, thus hugely reducing the efficacy of viral replication.[1,24] Decreased viral replication may possibly prevent excessive release of proinflammatory cytokines.[1]

Although it is an approved treatment for influenza, less preclinical support has been established for favipiravir to treat SARS-CoV compared to remdesivir.[24]

Clinical Studies

In an RCT comparing favipiravir with arbidol in 239 COVID-19 patients, the results indicated that favipiravir could be used in the treatment of moderate COVID-19 patients to halt disease progress into ARDS, shock and multiple organ failure. It was also noted that favipiravir group had a higher clinical recovery rate at day 7 (71.43%), than arbidol (55.86%), and the time of cough relief and fever reduction of the favipiravir group was significantly shorter than that of arbidol.[31] Another study on 80 moderate COVID-19 patients comparing favipiravir with LPV/r, the favipiravir group had a significant shorter viral clearance time of 4 days and higher improvement in chest imaging.[32] There are 8 registered studies on favipiravir for COVID-19, with 2 ongoing studies evaluating its safety and efficacy as treatment. There are no completed studies yet. DOH has expressed their interest in joining a clinical trial for Favipiravir offered by Japan.[33]

Recommended Dose

1600 mg 2x a day on day 1, then 600 mg 2x a day on days 2 to day 14 [32]

Adverse Effects

Some of the adverse effects are raised serum uric acid, abnormal liver function tests, psychiatric symptoms, and GI disturbance. It is contraindicated for known or suspected pregnant women and lactating women[32,34]

Conclusion

Antivirals may also have an immunomodulatory role for COVID-19 cytokine storm. More biomolecular studies have to be done to establish this effect.

REFERENCES:

1. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio*. 2018;9(2):e00221-18. Published 2018 Mar 6. doi:10.1128/mBio.00221-18
2. World Health Organization. "Solidarity" clinical trial for COVID-19 treatments. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
3. Jin, Y.; Yang, H.; Ji, W.; Wu, W.; Chen, S.; Zhang, W.; Duan, G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses* **2020**, *12*, 372.
4. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option [published online ahead of print, 2020 Feb 27]. *J Med Virol*. 2020;10.1002/jmv.25729. doi:10.1002/jmv.25729
5. National Center for Biotechnology Information. PubChem Database. Ritonavir, CID=392622, https://pubchem.ncbi.nlm.nih.gov/compound/Ritonavir (accessed on Apr. 7, 2020)
6. Malizia AP, Vioreanu MH, Doran PP, Powderly WG. HIV1 protease inhibitors selectively induce inflammatory chemokine expression in primary human osteoblasts. *Antiviral Res.* 74(1), 72–76 (2007).
7. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19 [published online ahead of print, 2020 Mar 18]. *N Engl J Med*. 2020;10.1056/NEJMoa2001282. doi:10.1056/NEJMoa2001282
8. Yuan, J., Zou, R., Zeng, L. *et al.* The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. *Inflamm. Res.* (2020). https://doi.org/10.1007/s00011-020-01342-0
9. Agrawal S, Goel AD, Gupta N. Emerging prophylaxis strategies against COVID-19. *Monaldi Arch Chest Dis*. 2020;90(1):10.4081/monaldi.2020.1289. Published 2020 Mar 30. doi:10.4081/monaldi.2020.1289
10. https://clinicaltrials.gov/ct2/show/NCT04321174 (Accessed 04/06/2020)
11. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug DiscovTher*. 2020;14(1):58–60. doi:10.5582/ddt.2020.01012
12. https://clinicaltrials.gov/ct2/show/NCT04321174 (Accessed 04/06/2020)
13. Zhang C, Huang S, Zheng F, Dai Y. Controversial treatments: an updated understanding of the Coronavirus Disease 2019 [published online ahead of print, 2020 Mar 26]. *J Med Virol*. 2020;10.1002/jmv.25788. doi:10.1002/jmv.25788
14. Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020 [doi: 10.1038/d41573-020-00016-0]
15. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252–256. doi:10.1136/thorax.2003.012658
16. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci*. 2020;248:117477. doi:10.1016/j.lfs.2020.117477
17. Morgenstern B, Michaelis M, Baer PC, Doerr HW, Cinatl J Jr. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. *BiochemBiophys Res Commun*. 2005;326(4):905–908. doi:10.1016/j.bbrc.2004.11.128
18. Feld JJ, Lutchman GA, Heller T, et al. Ribavirin improves early responses to peginterferon through improved interferon signaling. *Gastroenterology*. 2010;139(1):154–62.e4. doi:10.1053/j.gastro.2010.03.037

19. National Center for Biotechnology Information. PubChem Database. Ribavirin. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/37542.
20. Blaising J, Polyak SJ, Pécheur EI. Arbidol as a broad-spectrum antiviral: an update. *Antiviral Res*. 2014;107:84–94. doi:10.1016/j.antiviral.2014.04.006
21. Boriskin YS, Leneva IA, Pécheur EI, Polyak SJ. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. *Curr Med Chem*. 2008;15(10):997–1005. doi:10.2174/092986708784049658
22. Xu K, Chen Y, Yuan J, et al. Clinical efficacy of Arbidol in patients with 2019 novel coronavirus-infected pneumonia: a retrospective cohort study. Available at: https://ssrn.com/abstract=3542148 or http://dx.doi.org/10.2139/ssrn. 3542148.
23. Zhang J, Wang W, Peng B, Peng W, Zhang Y, Wang Y, Wan Y, Chang J, Mao L, Miao X, Zhou Y, Li Y, Hu Y, Hu B. Potential of arbidol for post exposure prophylaxis of COVID 19 transmission – preliminary report of a retrospective case control study. chinaXiv:202002.00065v1
24. Tu, Y.-F.; Chien, C.-S.; Yarmishyn, A.A.; Lin, Y.-Y.; Luo, Y.-H.; Lin, Y.-T.; Lai, W.-Y.; Yang, D.-M.; Chou, S.-J.; Yang, Y.-P.; Wang, M.-L.; Chiou, S.-H. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. *Int. J. Mol. Sci.* **2020**, *21*, 2657.
25. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. *Chembiochem*. 2020;21(5):730–738. doi:10.1002/cbic.202000047
26. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19 [published online ahead of print, 2020 Mar 5]. *Travel Med Infect Dis*. 2020;101615. doi:10.1016/j.tmaid.2020.101615
27. Khalili JS, Zhu H, Mak A, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: Groundwork for evaluation concerning COVID-19 [published online ahead of print, 2020 Mar 30]. *J Med Virol*. 2020;10.1002/jmv.25798. doi:10.1002/jmv.25798
28. https://clinicaltrials.gov/ct2/show/NCT04292730. Accessed on Aprill 6, 2020
29. https://clinicaltrials.gov/ct2/show/NCT04292899. Accessed on Aprill 6, 2020
30. Cunja JP. RxList. Remdesivir. Available from: https://www.rxlist.com/consumer_remdesivir_rdv/drugs-condition.htm.
31. Chen C, Huang J, Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. medRxiv preprint. Available from: doi: https://doi.org/10.1101/2020.03.17.20037432. Accessed on: March 27, 2020
32. Cai Q, Yang M, Liu D, et al. Experimental treatment with Favipiravir for COVID-19: an open-label control study *Engineering* 2020. In press. Available from: https://doi.org/10.1016/j.eng.2020.03.007.
33. Reuters. Japan to boost Avigan drug stockpile as part of coronavirus stimulus. Available from: https://news.abs-cbn.com/business/04/05/20/japan-to-boost-avigan-drug-stockpile-as-part-of-coronavirus-stimulus. Accessed on: March 6, 2020
34. Medical Information Center Taisho Toyama Pharmaceutical Co., Ltd. Avigan. Available from: https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw.

6. JAK 1 INHIBITOR (BARICITINIB)

Introduction

Baricitinib was licensed in 2018 for treating rheumatoid arthritis with excellent clinical response and no significant safety concerns.[1,2,3]

Mechanism of Action

Baricitinib has two mechanisms of action.

1. It is a selective inhibitor of Janus kinases (Jaks) 1 and 2. Janus family of kinases comprises four members: Tyk2, Jak1, Jak2 and Jak3, which associate with cytokine receptors of interleukins, interferons, and colony stimulating factor, as well as classic hormones such as erythropoietin, prolactin and growth hormone. Upon ligand binding, Jaks phosphorylate the cytokine receptors and induce recruitment of other cellular transcription factors which directly initiate gene expression and cytokines production such as interferon alpha, interferon gamma and IL-6. Inhibition of Jaks 1 and 2 by baricitinib blocks the production of these cytokines thereby dampens inflammatory response by the host.[4,5]
2. It also effectively inhibits certain protein kinases (AP2-associated protein kinase 1(AAK-1) and cyclin-G associated kinase (GAK)) and thus inhibits viral endocytosis into the host cells.[4,5]

With the evidence of the advantageous action of baricitinib on viral entry and cytokine outbreak, it has been suggested that it could be used in an appropriate patient population with COVID-19 acute respiratory disease, to reduce both the viral entry and the aberrant inflammatory response in patients.[6]

Compared to the other JAKinibs, baricitinib with its high affinity for AAK1 is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile. In addition, the potential for combination therapy with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. There is the potential for combining baricitinib with the direct acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug metabolizing enzymes.

Clinical Studies

To date, no published clinical trial evidence for baricitinib as a treatment for COVID-19 is available. A non-peer reviewed article on in vitro testing of anti-SARS-CoV-2 activities of several drugs reported that baricitinib showed no inhibitory activities against SARS-CoV-2 at the concentration of 3 μM or 3.2 μM.[8]

Three clinical trials of baricitinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future. (Appendix K)

Dosage

Adult: 2-4mg once daily for 10-14 days
Pediatric: Safety and efficacy not established[9]

Adverse Effects

The majority of adverse reactions are mild, such as upper respiratory tract infections. However, there is a Black Box Warning regarding: (1) Serious and sometimes fatal infections may develop owing to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens reported; may cause reactivation of latent TB or viral infections; (2) Lymphoma and other malignancies observed; (3) Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), observed at an increased incidence in patients treated with baricitinib.[9]

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy and safety of baricitinib to treat COVID-19, although the drug appears to be relatively safe and well tolerated as treatment for rheumatoid arthritis. Results and findings from the **3** ongoing studies of baricitinib for COVID-19 will help determine whether it can be used more widely in this setting.

REFERENCES:

1. Bechman K, Subesinghe S, Norton S, Atzeni F, Galli M, Cope AP, Winthrop KL, Galloway JB. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatology (Oxford). 2019 Oct 1;58(10):1755-1766. doi: 10.1093/rheumatology/kez087;
2. Kunwar S, Collins CE, Constantinescu F. Baricitinib, a Janus kinase inhibitor, in the treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. Clinical Rheumatology. 2018 Oct;37(10):2611-2620. doi: 10.1007/s10067-018-4199-7 Epub 2018 Jul 13;
3. Masayoshi Harigai,Tsutomu Takeuchi,Josef S. Smolen, et al. Safety profile of baricitinib in Japanese patients with active rheumatoid arthritis with over 1.6 years median time in treatment: An integrated analysis of Phases 2 and 3 trials. Modern Rheumatology. 2020; 30(1), https://doi.org/10.1080/14397595.2019.1583711;
4. Ennio Giulio Favalli, et al., Autoimmunity Reviews, https://doi.org/10.1016/j.autrev.2020.102523;
5. W. Zhang, Y. Zhao, F. Zhang, et al., The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China, Clinical Immunology. https://doi.org/10.1016/j.clim.2020.108393;
6. Richardson P. Griffin I, Tucker C. Smith D, Oechsie O. Phelan A, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020 Feb 15;395(10223): e30-e31. Doi: 10.1016/SO140-6736(20)30304-4 Epub 2020 Feb 4;
7. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020 Feb 27; S1473-3099(20)30132-8. doi.org/10.1016/S1473-3099(20)30132-8 Epub 2020 Apr 20;
8. Ge Y, Tian T, Huang S et al. A data driven drug repositioning framework discovered potential therapeutic agent targeting COVID-19. BioRxiv March [Preprint]. Accessed 29 March 2020. https://www.biorxiv.org/content/10.1101/2020.03.11.986836v1.full.pdf+html;
9. Baricitinib (Rx) Drugs and Diseases, Medscape.

7. CCR5 INHIBITOR (LERONLIMAB)

Introduction

Leronlimab (Pro 140) is an investigational drug primarily studied for HIV infection and recently under Emergency Investigational New Drug (eIND) for COVID-19 by the US FDA.[1]

Mechanism of Action

It belongs to the drug class known as the CCR5 antagonists. C-C chemokine receptor type 5 (CCR5) is a co-receptor of the CD 4 receptor on the surface CD 4 cells. It blocks the entry of some viruses particularly HIV and potentially SARS-CoV-2, preventing its entry into and activation of CD4 cells. Thus it mitigates the release of inflammatory cytokines such as IL-6 and TNF alpha and the ensuing " cytokine storm".[1]

Clinical Studies

As of this time, there is one ongoing study to evaluate the efficacy and safety of Leronlimab for mild to moderate COVID 19.[2]

Adverse Effects

Since Leronlimab is still under study, the present information on its side effects may yet be incomplete. As more trials conducted, information on these adverse reactions will be gathered.[1]

Conclusion

Leronlimab is an eIND US FDA for treatment of mild to moderate COVID-19 and available to its participation study institutions.

REFERENCES:

1. https://aidsinfo.nih.gov/drugs/423/leronlimab/0/patient
2. https://clinicaltrials.gov/ct2/show/record/NCT04343651?term=leronlimab&cond=covid+19&draw=2&rank=1

8. MESENCHYMAL STEM (STROMAL) CELLS

Introduction

Mesenchymal stem cells (MSC) are non-hematopoietic, multipotent stem cells with the capacity to differentiate into mesodermal lineage such as osteocytes, adipocytes and chondrocytes as well ectodermal and endodermal lineages. The International Society for Cellular Therapy (ISCT) states that MSC must express CD29, CD44, CD73, CD90, CD105 and lack expression of CD14, CD19, CD45, CD79, or HLA-DR surface molecules.[1]

Mechanism of Action

MSC may have beneficial effects for preventing or attenuating the cytokine storm. MSCs play a positive role mainly in two ways: immunomodulatory effects and differentiation abilities. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells including T cells, B cells, dendritic cells, macrophages and natural killer cells leading to immunomodulation. Immunomodulatory effects are attained through the following possible mechanisms through the release of transforming growth factor alpha (TGF-alpha), hepatocyte growth factor (HGF), nitric oxide, indoleamine 2,3-dioxygenase (IDO), intracellular adhesion molecule 1 (ICAM 1), vascular cell adhesion molecule 1 (VCAM 1) and others. It may also inhibit proliferation of T-cells in reaction to alloantigens and mitogens.[2,3,4]

Clinical Studies

There is currently only 1 pilot trial published using intravenous MSC in 7 patients with COVID-19 infected pneumonia who received one dose of stem cell therapy, compared to 3 patients in the control group (3 serious) who did not. Limitations of this study include the small sample size and short-term follow-up.[5]

There are 14 other studies listed in ClinicalTrials.gov using MSC for COVID-19 that are either recruiting subjects (5); have not yet started (8), and withdrawn (1).[6] (Appendix M)

Adverse Reactions

Safety and effectiveness of MSCs have been documented in several clinical trials.[7,8] However, numerous complications have been reported from improper application of stem cells.[9] Therefore, quality preparation of the stem cells is of paramount importance. Assurance for safety should include: (1) source should be from legitimate labs compliant with the FDA standards; (2) strict screening of donors, (3) product must be analyzed for cell viability, quality and sterility and must meet the highest standards, (4) cell passage numbers should be limited to increase potency and decrease cell size.[10]

Also, during IV infusion, all precautions should be taken to prevent pulmonary or other organ embolization. Patients should be monitored for allergic reactions especially when using allogeneic products. [10]

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy of MSC to treat COVID-19 infection. MSC appear to be relatively safe. One of the main restrictions in this approach is obtaining the source of clinical-grade MSCs and subsequently the speed of preparation for clinical usage.

REFERENCES:

1. Dominici, M., Blanc, K. Le, Mueller, I., Marini, F. C., Krause, D. S., Deans, R. J. Horwitz, E. M. 2006. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 8(4), 315–317. https://doi.org/10.1080/14653240600855905
2. Wilson, JG, Liu KD, Zhuo NJ, Caballero L, McMillan M, Fang XH, et al. 2015. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respiratory Medicine, 3:24-32.
3. Hashmi S, Ahmed M, Murad MH, Litzow MR, Adams RH, Ball LM, et al. 2016. Survival after mesenchymal stromal cell therapy in steroidrefractory acute graft-versus-host disease: systematic review and meta-analysis. Lancet Haematology, 3:E45-E52.
4. Abraham A, Krasnodembskaya A Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. Stem Cells Transl Med 2020; 9:28-38.
5. Leng Z, Zhu R, Hou W. Transplantation of ACE2 Mesenchymal stem cells improves the outcomes of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216-228.
6. https://clinicaltrials.gov/ct2/results?cond=COVID&term=mesenchymal+stem+cells&cntry=&state=&city=&dist=
7. Kamen DL, Nietert PJ, Wang H, Duke T, Cloud C, Robinson A, et al. 2018. CT-04 Safety and efficacy of allogeneic umbilical cord-derived mesenchymal stem cells (MSCs) in patients with systemic lupus erythematosus: results of an open-label phase I study. Lupus Science & Medicine, 5:A46-A47
8. Golchin, A., Farahany, T. Z., Khojasteh, A., Soleimanifar, F., & Ardeshirylajimi, A. 2018. The clinical trials of Mesenchymal stem cell therapy in skin diseases: An update and concise review. Current Stem Cell Research & Therapy, 14(1), 22–33. https://doi.org/10.2174/1574888x13666180913123424.
9. Bauer G, Elsallab M, Abou-El-Enein M. Concise Review: A comprehensive analysis of reported adverse events in patients receiving unproven stem cell based interventions. Stem Cells Transl Med 2018; 7:676-685.
10. Atluri S, Manchikanti L, Hirsch JA.Expanded Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) as a Therapeutic Strategy in Managing Critically Ill COVID-19 Patients: The Case for Compassionate Use. Pain Physician. 2020 Mar;23(2):E71-E83.

9. BCG VACCINE

Introduction

Vaccines induce direct protection from the antigens by stimulating our innate and adaptive immune system. It may also be used for non-specific stimulation of our immune system inducing non-specific protection.[1]

Mechanism of Action

The BCG vaccine reprograms monocytes, leading to an up-regulation of IL-1B a proinflammatory cytokine associated with induction of trained immunity. In vivo, this leads to protection against non-related viral infections, a key role for IL-1B as a mediator of trained immunity responses.[2,3]

Aside from its usage to protect and reduce the incidence of mycobacterial infection (e.g. Tuberculosis), BCG has been used to fight off superficial bladder carcinoma.[4,5] Intravesical instillation of BCG into the bladder does not destroy the tumor directly but increase a local immune response against the tumor.

Clinical Studies

An epidemiological paper was published describing the effect of the presence or absence of universal BCG vaccine policies of countries affected by COVID-19. It was found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies.[2] Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population.[2]

Conclusion

There are no randomized controlled trials showing the impact of BCG usage in COVID-19 nor how fast immune responses develop that can protect against COVID-19.

There is no evidence at the moment to support the use of BCG in the treatment of COVID-19.

REFERENCES:

1. Benn CS, Netea MG, Selin LK, Aaby P. A small jab – A big effect: nonspecific immunomodulation by vaccines. Trends In Immunology, September 2013, Vol34, No9, p31-439.
2. Miller A, Reandelar, et al.Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study; Department of Biomedical Sciences, NYIT College of Osteopathic Medicine, New York Institute
3. Arts RJW, Simone J.C.F.M. Moorlag et.al., BCG Vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity, cell and host & microbe, Cell press 2017.12.010
4. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, et al. EAU guidelines of non-muscle invasive urothelial carcinoma of bladder: update 2013. EUR Urol 2013;64:639–53.
5. Moshe Tishler, Chapter 14 BCG Infection and Autoimmunity Elsevier 2015

10. SUPPLEMENTS

a. VITAMIN C

Introduction

Ascorbic acid is a water soluble vitamin with antioxidant and immunomodulatory properties.[1]

Mechanism Of Action

Vitamin C has immunomodulatory effects on monocytes and macrophages. It can inhibit monocyte death (FAS-mediated apoptosis), diminish secretion of pro-inflammatory cytokines (IL-6, and TNF), and enhance phagocytosis.[2]

Vitamin C also neutralizes reactive oxidants and improves chemotactic stimuli. It can accumulate in phagocytic cells which leads to enhanced phagocytosis of microbes and generation of reactive oxygen species (ROS).[3]

In vitro studies have indicated that incubation of Vitamin C with lymphocytes - promotes proliferation, and enhanced antibody generation. T-regulatory cell activity may also be regulated via the inhibition of expression of distinct transcription factors, cytokines and antigen.[4]

Vitamin C has an effect on the proliferation of human natural killer (NK) cells resulting in higher cell numbers.[5]

Giving Vitamin C early prevents sepsis-induced cytokine surge that activate and sequester neutrophils in the lungs thus damaging alveolar capillaries. This leads to alveolar fluid clearance by preventing activated neutrophil accumulation in alveolar spaces.[6]

Clinical Studies

As of this time, there are 3 ongoing clinical trials on the use of high dose Vitamin C for COVID-19. (Appendix N)

Adverse Effects

The side effects of giving high dose Vitamin C are calcium oxalate nephropathy and elevation in blood sugar.[7]

Recommended Dose

Not established as of this time.

Conclusion

There is currently no evidence on the use of Vitamin C in the treatment of COVID-19 as clinical trials are still ongoing.

REFERENCES:

1. Mousavi S., Bereswill,S., Heimesaat M. Immunomodulatory and antimicrobial effects of vitamin C, Eur J Microbiol Immunol 2019 Oct 3: 9(3):73-79]
2. Perez-Cruz I, Carcamo JM, Golde DW. Vitamin C inhibits FAS-induced apoptosis in monocytes and U937 cells. Blood. 2003;102(1):336–43.]
3. Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017;9(11).]
4. Gao YL, Lu B, Zhai JH, Liu YC, Qi HX, Yao Y, et al. The parenteral vitamin C improves sepsis and sepsis-induced multiple organ dysfunction syndrome via preventing cellular immunosuppression. Mediators Inflamm. 2017;2017:4024672.]
5. Huijskens MJ, Walczak M, Sarkar S, Atrafi F, Senden-Gijsbers BL, Tilanus MG, et al. Ascorbic acid promotes proliferation of natural killer cell populations in culture systems applicable for natural killer cell therapy. Cytotherapy. 2015;17(5):613–20
6. Fowler A.A., Truwit J.D., Hite R.D., Morris P.E., DeWilde C., Priday A., Fisher B., Thacker L.R., Natarajan R., Brophy D.F., et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI Randomized Clinical Trial. JAMA. 2019;322:1261–1270.]
7. Padayatty SJ, Sun AY, Chen Q, Espey MG, Drisko J, Levine M. Vitamin C: Intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One. 2010;5:e11414. doi: 10.1371/journal.pone.0011414.

10. SUPPLEMENTS

b. ZINC

Introduction

Zinc (Zn) is an essential trace mineral with antiviral properties. There is no specialized Zn storage system in the body therefore a daily intake is needed to achieve a steady state.[1]

Mechanism Of Action

Zinc inhibits the RNA synthesizing activity of SARS-COV replication and transcription complex (RTC). In vitro studies show Zn inhibits the SARS-COV RNA dependent RNA polymerase (RdRp) activity during the elongation phase of RNA synthesis by affecting template binding. It also inhibits both proper proteolytic processing of replicase polyproteins and RdRp activity.[1]

Clinical Studies

There is an ongoing study on the protective effects of IV zinc against organ damage in coronavirus. [2]

Recommended Dose

Not yet established for COVID-19.

Adverse Effects

Zinc toxicity can manifest as nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headache. Given in high doses it can affect copper status and reduced iron function.[3]

Conclusion

There is only one ongoing study on zinc for COVID-19. There is currently no evidence for the effectiveness of zinc as an adjunctive treatment in patients with COVID-19.

REFERENCES:

1. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. Adv Nutr. 2019;10(4):696–710. doi:10.1093/advances/nmz013
2. Ischia J, Patel O. Protective effects of IV Zinc against organ damage in Coronavirus. https://about.unimelb.edu.au/newsroom/news/2020/april/world-first-trial-to-test-benefit-of-intravenous-zinc-in-covid-19-fight
3. Saper RB, Rash R. Zinc: an essential micronutrient. Am Fam Physician. 2009;79(9):768–772.

10. SUPPLEMENTS

c. MELATONIN

Introduction

Melatonin (5 – methoxy – N – acetyltryptamine) is a hormone secreted by the pineal gland. It is given primarily for insomnia but recent researches showed that it has anti-inflammatory and anti-oxidant effects.[1]

Mechanism Of Action

As an anti-inflammatory agent, melatonin downregulates Nuclear Factor Kappa-B (NFK-B), and, through Sirtuin-1, down regulates proinflammatory polarization of macrophages, both resulting to an anti-inflammatory response.[2,3,4]

As an anti-oxidant, melatonin up-regulates anti-oxidative enzymes (superoxide dismutase), downregulates pro-oxidative (nitric oxide synthase), and functions as a free-radical scavenger[1,5]

Lastly, melatonin improves proliferation and maturation of NK cells, T and B lymphocytes.[6]

Clinical Studies

Currently, there are no studies on the use of melatonin for COVID-19.

Adverse Effects

Adverse effects include fatigue, changes in mood, psychomotor or neurocognitive performance.[7]

Conclusion

There is no available evidence as to the use of melatonin in COVID-19.

REFERENCES:

1. Reiter R.J., Ma.Q.Sharma R. Treatment of ebola and other infectious diseases: melatonin “goes”viral” Melatonin Res.2020;3:43-57.
2. Rui Zhang, Xuebin Wang, et.al. COVID-19: Melatonin as potential adjuvant treatment, Life Sci. 2020 Mar 23:117583.
3. Ling Y.,et al. MicroRNA-494 inhibition alleviates acute lung injury through Nrf2 signaling pathway via NQO1 in sepsis-associated acute respiratory disease syndrome. Life Sci. 2018;210:1-8.
4. Hardeland, R., Melatonin and inflammation—story of a double-edged blade, J. Pineal Res., 2018, vol. 65, no. 4, e12525.
5. Ahmadi Z., et.al. Melatonin as a potential modulator of Nrf2. Fund. Clin. Pharmacol. 2020;34:11-19.
6. Wu X., et al. Melatonin alleviates radiation-induced lung injury via regulation of miR-30e/NLRP3 axis. Oxidative Med. Cell. Longev. 2019;2019:4087298.
7. Foley, H.M.; Steel, A.E. Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. *Complement. Ther. Med.* **2019**, *42*, 65–81.

10. SUPPLEMENTS

d. QUERCETIN

Introduction

COVID-19 disease mortality rate seems to have an association with patients with advanced chronological age.[1]These patients have an increased number of senescent lung cells, which are the host target for COVID-19 viral infection.[2]

Quercetin is a pigment derived from plants that is in the bioflavonoid category.[3] Foods and drinks that contain Quercetin include berries, apples, citrus fruits, kale, tomatoes, onions, buckwheat, red wine, and black tea. It is also found in herbal remedies, such as ginkgo biloba and St John's wort. It is reported to possess antioxidant, anti-inflammatory and immune regulatory effects. It is also considered a senolytic, meaning it can both get rid of bad cells and help old cells.[3]

These senolytic drugs could be beneficial for the treatment and/or prevention of COVID-19 disease.

Mechanism of Action

Two host receptors, CD 26 and ACE-2, have been associated with COVID-19 and senescence. Activation of these receptors in senescent cells have been noted to produce inflammatory cytokines such as a result of the senescence-associated secretory phenotype (SASP), including IL-6.

A recent study, using supercomputer-based *in silico* drug-docking to the COVID-19 viral spike protein identified Quercetin as a potential binding partner, to reduce virus-host interactions, with ACE-2.[4]

Hence blocking of CD26 and ACE-2 receptors with Quercetin may have an anti-inflammatory effect.

Clinical Studies

No clinical studies are available at this time.

Recommended Dose

Still to be established.

Adverse Effects

May cause headaches and tingling sensation of arms and legs

Conclusion

There is no evidence on the efficacy of Quercetin in treating COVID-19 patients. Clinical trials in humans are needed.

REFERENCES:

1. Sargiacomo C, Sotgia F, Lisanti MP. COVID-19 and chronological aging: senolytics and other anti-aging drugs for the treatment and prevention of corona virus infection?. Aging (Albany NY). 2020 March 30. https://doi.org/10.18632/aging.103001 [Epub ahead of print]
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, et al. Clinical course and rishk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-62 https://doi.org/10.1016/S0140-6736(20)30566-3 [PubMed]
3. Anand AV, Arulmoli R, Parasuraman S. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev. 2016;10(20):84–89. doi:10.4103/0. 973-7847.194044
4. Smith M, Smith JC. Repurposing Therapeutics for COVID-19: Supercomputer-Based Docking to the SARS-CoV-2 Viral Spike Protein and Viral Spike Protein-Human ACE2 Interface. 2020. ChemRxiv. https://doi.org/10.26434/chemrxiv.11871402.v4

CONCLUDING REMARKS

There is no single immunomodulator nor a combination that stands out as the most effective therapy in dealing with the COVID-19 pandemic. As we state that some of the immunomodulators have not yet proven to be effective, with the results of ongoing studies we are hopeful that we get positive answers from these researches. Presently many drug researches are ongoing and their results will validate which immunomodulators will best be given for patients who are afflicted with this disease.

As the COVID-19 phenomenon continues, we are tasked to battle the ensuing cytokine storm. It is our society's challenge to continue to review the literature that is available. It is our goal to present the evidence and disseminate it for better healthcare.

This review was limited to published or available data where the English language was used. There may be excellent researches done that were not included in this review if these studies used another language.

We present our first version dated April 20, 2020.

Appendix A. Intravenous Immunoglobulin (IVIG) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Cao W, et al.	Case series (China)	IVIG	Standard care	Patients with COVID 19, severe type	Improvement in clinical status and laboratory parameters	3 cases successfully treated by high-dose IVIG at early stage of clinical deterioration, so they recommend-ed that timing of IVIG administra-tion is critical	Published	https://academic.oup.com/ofid/article/7/3/ofaa102/5810740
Hu H, et al.	Case report (China)	Methylpredni solone + IVIG + Nor-epinephrine + Toracemide + Furose-mide + Milrinone + Sulbactam + Pantopra-zole	Standard care	Patient with pulmonary infection, enlarged heart, pleural effusion & positive coronavirus nucleic acid test	Improvement in clinical status & laboratory parameters	Suggested that early Glucocortisco steroid (GC) + IVIG may be of important value to this type of patient	Published	https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa190/5807656
Zhou Z, et al.	Prospective cohort study (China)	IVIG short-term plus moderate-dose corticosteroid (160 mg/d)	N/A	COVID-19 patients	Improvement in clinical status and laboratory parameters	all patients achieved significant improvement in terms of vital signs, blood work, and the APACHE Ⅱ scores	Pre-print	https://www.preprints.org/manuscript/202003.0065/v1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Shao Z, et al.	Multicenter retrospective cohort study (China)	IVIG Subgroups: • >15g/day • <15g/day • >7 days • ≤7 days	Standard care	Patients with COVID 19 Severe type Critical type ≥18 y/o	28-day & 60-day mortality	The 28-day & 60-day mortality did not improve between the IVIG group & non-IVIG. IVIG significantly decrease 28-day mortality of patients in critical type but not in the 60-day mortality. High dose IVIG (>15 g/d) significantly reduced 28 & 60-day mortality. Early use of IVIG (≤ 7d) significantly reduced the 60-day mortality but not the 28-day mortality.	Pre-print	https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v1.full.pdf
NCT04261426	Phase 2/3 single-center, randomized, open-label, controlled study (China)	IVIG 0.5 g/kg/d for 5 days	Standard care	Patients with COVID 19 ≥18 y/o	Clinical improvement of 7-point scale, lower Murray lung injury score on D7 &14	APACHE Ⅱ scores	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04261426?term=NCT04261426&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04350580	Randomized, parallel assignment (Paris)	IVIG started between 24 & 72 hours after start of mechanical ventilation	Placebo (sodium chloride 0.9%)	Patients with COVID 19 & ARDS meeting the Berlin criteria ≥18 y/o	Ventilator-free days	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04350580?term=intravenous+immunoglobulin&cond=COVID-19&draw=2&rank=4

Appendix B. Convalescent Plasma (CP) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Duan K, et al.	Case series (China)	1 dose of 200 ml CP with neutralizing antibody titers >1:640 given from symptom onset to 11 to 20 days	None	Patients with severe COVID 19	Safety of CP transfusion; improvement of clinical symptoms & laboratory parameters within 3 days after CP transfusion	No serious adverse events; symptoms of 10 patients improved in 1-3 days; reduced pulmonary lesions on chest CT; amelioration of routine laboratory criteria & pulmonary function; Increase IgG titers & (-) SARS-CoV-2 RNA.	Completed	https://www.pnas.org/content/early/2020/04/02/2004168117

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Shen C, et al.	Case series (China)	CP derived from donors by apheresis with the SARS-COV-2 specific IgG ELISA titer >1:1000 & neutralizing antibody titer >40 + anti-viral agents & steroid	None	Critically ill patients with COVID 19 in 1. respiratory failure requiring mechanical ventilation 2. shock with vasopressor therapy & elevated lactate levels 3. failure of other organs requiring admission to ICU	Before and after CP transfusion: 1.Changes in body temperature 2. Sequential Organ Failure Assessment (SOFA) score 3. PaO2/FiO2 4. Viral load, serum ab titer, routine blood biochemical index 5. ARDS & ventilatory & extra-corporeal membrane oxygenation (ECMO) support	After CP: 1. Body temperature declined to normal range on D3 2. SOFA score decreased 3.PaO2/FiO2 improved in D7 4. CRP, procalcitonin & IL 6 decreased 5. ARDS resolved in 4 patients in D12; 3 patients weaned from mechanical ventilator after 2 weeks, 3 patients were discharged & 2 are in stable 37 days post transfusion	Completed	https://www.ncbi.nlm.nih.gov/pubmed/32219428

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04340050	Interventional Open Label	CP	None	Patients with COVID 19	Feasibility of performing study pathway (consenting convalescent donors), harvesting CP, FDA eIND application, CP administra-tion, type of respiratory support	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04340050
NCT04342182	Randomized comparative trial	CP	Standard care	Patients with COVID 19	Overall mortality until discharge or maximum of 60 days after admission	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04342182
NCT04332835	Randomized controlled, open Label, parallel assignment	CP + Azithromycin + HCQ	Azithromycin + HCQ	Patients with COVID 19	Change in the following: -viral load, -IgM COVID 19 titers, -IgG COVID 19 titers	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04332835
NCT04264858	Non-randomized, open label, parallel assignment (China)	CP	γ globulin	Patients with COVID 19	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04264858

Appendix C. Corticosteroids (CS) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Wang Y, et al.	Observation-al (China)	Methyl-prednisolone	Standard care	Severe COVID 19 pneumonia	Clinical & radiographic outcome of treatment w/ or w/o CS	Early short term & low dose CS: faster clinical improvement & absorption of lung focus	Completed	https://www.researchgate.net/publication/339892221
NCT04273321	Randomized, Controlled, open label, single group, prospective	Methyl-prednisolone	Standard Care	COVID 19 pneumonia	Incidence of treatment failure in 14 days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04273321
NCT04323592	Non-randomized, open label, phase II/III, single group assignment	Methyl-prednisolone	Standard care	Severe COVID 19 with acute respiratory syndrome	Death or ICU admission or mechanical ventilation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04323592?term=steroid&cond=COVID+19&draw=2&rank=5
NCT04327401	Randomized, interventional open label, parallel assignment	Dexametha-sone	Standard care	COVID 19 associated ARDS	Ventilator free days	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04327401?term=corticosteroids&cond=covid+19&draw=2&rank=3
NCT04325061	Randomized, interventional open label, parallel assignment	Dexametha-sone	Standard care	COVID 19 ARDS	60-day mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04325061?term=corticosteroids&cond=covid+19&draw=2&rank=4

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT02735707	Randomized, embedded, multifactorial platform trial	Hydro-cortisone, Macrolide & other antibiotics, Oseltamivir, LPV/r, HCQ, IFN β1a, Anakinra	Hydro-cortisone, Macrolide & other antibiotics, Oseltamivir, LPV/r, HCQ, IFN β1a, Anakinra	Community Acquired Pneumonia, Influenza, COVID 19	All cause mortality; Days alive & outside of ICU	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT02735707?term=corticosteroids&cond=covid+19&draw=2&rank=5&view=record
NCT04329650	Randomized, open label, parallel assignment	Siltuximab	Methyl-prednisolone	COVID 19 Pneumonia	Proportion of patients requiring ICU admission at anytime during the study period	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04329650?term=corticosteroids&cond=covid+19&draw=2&rank=1
NCT04348305	Randomized controlled, parallel assignment	Hydrocorti-sone	Placebo	COVID-19 with severe hypoxia	Days alive without life support at D28	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04348305?term=steroid&cond=covid+19&draw=2&rank=1&view=record
NCT04244591	Randomized controlled, open Label multicenter	Methypred-nisolone	Standard care	COVID-19 Critically Ill patient with severe acute respiratory failure	Lower Murray Lung Injury score D7 & 14 after randomiza-tion	NA	Completed	https://clinicaltrials.gov/ct2/show/NCT04244591?term=steroid&cond=covid+19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Zhou ZG, et al	Case series	Methylpredni solone + IVIG	NA	Patients with COVID 19	Reversion of continued deterioration of COVID-19 patients.	Short-term moderate-dose CS + IVIG is effective for reversing the continued deterioration of COVID-19 patients.	Completed	https://www.preprints.org/manuscript/202003.0065/v1

Appendix D. Hydroxychloroquine (HCQ) and Chloroquine (CQ) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Chen J, et al.	Pilot Study, randomized Control	HCQ	Standard care	Patients with COVID 19	Negative conversion rate of COVID 19 nucleic acid in respiratory pharyngeal swab on D7 after randomiza-tion.	No significant difference in the following parameters: (-) nucleic acid throat swab; median duration from hospitalize-tion to virus nucleic acid negative conservation; median time for body temp normaliza-tion; radiological progression in CT images	Published	http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Gao J, et al.	Not stated	CQ	Standard care	Patients with COVID 19	Clinical improvement	CQ reduced symptom duration, inhibition in pneumonia exacerbation, improved lung function, virus negative conversion w/o severe side effects	Completed	https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article
Mahévas M, et al.	Observation-al	HCQ in 1st 48 hours after hospitalisa-tion	Standard care	COVID-19 pneumonia 18-80 y/o	Transfer to ICU within 7 days of inclusion and/or death from any cause	Death or transfer to ICU: HCQ (20.2%) Non-HCQ (22.1%); Death within 7 days: HCQ (2.8%) Non-HCQ (4.6%); Harm with QTc prolongation (8), AV block (1), LBBB (1)	Completed	https://doi.org/10.1101/2020.04.10.20060699
Chorin E, et al.	Retrospective Observation-al	HCQ & Azithromycin	None	Patients with COVID-19 >18 y/o	Change in QT interval	Prolonged QTc (11%)	Completed	https://doi.org/10.1101/2020.04.02.20047050
Molina JM, et al.	Prospective Observation-al	HCQ 600 + Azithromycin	None	Severe COVID-19 Adults	Virologic presence after D6-7 of treatment	(+) virus in NPS on D7 of treatment (8/10)	Completed	https://doi.org/10.1016/j.medmal.2020.03.006

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Zhaowei C, et al.	Randomized parallel assignment	HCQ	Standard care	COVID-19 pneumonia >18 y/o (mild - SaO2/SPO2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg)	Normalization of body temperature, cough relief, CT changes	Normalization of body temperature: HCQ (2.2 days); Cough relief HCQ (2.0 days); Progression to severe illness: HCQ (0); CT improvement: HCQ (25); Adverse effects with HCQ: rash (1), Headache (1)	Completed	https://doi.org/10.1101/2020.03.22.20040758
Gautret P, et al.	Prospective observational	HCQ + Azithromycin	None	Patients with COVID-19 >18 y/o	Disease progression, need for oxygen, ICU admission	Death (1); Discharge (81.25%); Virologic clearance on day 7 (83%); Mean length hospital stay (5 days); O2 therapy (12); Transferred to ICU (3) AE: nausea, vomiting, diarrhea	Completed	https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Gautret P, et al.	Non-randomized, open label	HCQ; HCQ + Azithromycin	Standard care	Hospitalized COVID 19 patients >12 y/o	Viral clearance at D6 post inclusion	Viral clearance at D6: 100% with HCQ + Azithromycin; 57.1% with HCQ; 12.5% in control. Effect is reinforced by Azithromycin	Ongoing study	https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub
NCT04307693	Randomized controlled	HCQ	LPV/r	Patients with COVID 19	Laboratory detection of viral load, time to clinical improvement, time to death or ICU unit care, mechanical ventilation, O2 support	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693
NCT04318444	Randomized Controlled	HCQ	Placebo	Household or in-hospital contact with COVID 19 patients	COVID 19 symptoms; confirmed COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04318444
NCT04303507	Randomized controlled	HCQ	Placebo	Participants without previous COVID19	Duration of COVID 19; number of asymptoma-tic/ symptomatic cases; symptom severity	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04303507

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04315896	Randomized controlled	HCQ	Placebo	Participants with confirmed COVID 19 and serious respiratory impairment	All-cause mortality; length of hospital stay; mechanical ventilation	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04315896
NCT04323631	Randomized controlled	HCQ	Standard care	Patients with COVID 19	Number of patients with severe infection or death	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04323631
NCT04318015	Randomized controlled	HCQ	Placebo	Health profession-als that had contact with COVID 19 patients	Number of symptomatic cases; absenteeism complication	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04318015
NCT04316377	Randomized controlled	HCQ	Standard care	Patients with COVID 19 hospitalized and with serious respiratory impairment	Mortality, length of hospital stay; mechanical ventilation; length of ICU stay; laboratory detection of viral load	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04316377
NCT04319900	Randomized controlled	CQ + Favipiravir	Favipiravir	Patients with COVID 19	Time to symptoms improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04319900
NCT04321616	Randomized controlled	HCQ	Remdesivir	Hospitalized patients with COVID 19	All-cause mortality, ICU care, mechanical ventilation	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04321616

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04308668	Randomized controlled	HCQ	Placebo	Participants exposed to COVID 19 patients	Confirmed COVID19 cases; COVID 19 Hospital stay; Mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04308668
NCT04321993	Non-randomized controlled	HCQ	LPV/r, Baricitinib, Sarilumab	Hospitalized participants confirmed COVID 19 with moderate/ severe disease	Clinical status, mortality, length of disease	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04321993
ChiCTR2000030718	Randomized controlled	HCQ	Standard care	Patients with COVID 19	Mortality, severity of respiratory impairment, length of disease, laboratory detection of viral load, O2 supple-mentation duration	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=50843
ChiCTR2000029988	Randomized controlled	CQ	Standard care	Patients with COVID 19	Mortality rate, length of hospital stay; length of ICU stay, length of mechanical ventilation	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49218

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000029939	Randomized controlled	CQ	Standard care	Patients with COVID 19	Specific mortality rate, length of hospital stay	NA	Recruiting	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029939
ChiCTR2000029935	Single arm study	CQ	Standard care	Patients with COVID 19	Specific mortality rate	NA	Recruiting	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029935
ChiCTR2000029868	Randomized controlled	HCQ	Standard care	Patients with COVID 19	Laboratory detection of viral load	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49524
ChiCTR2000029741	Randomized controlled	HCQ	LPV/r	Participants with confirmed COVID 19	Mortality rate; length of hospital stay; proportion of critical cases	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49263
ChiCTR2000029740	Randomized controlled	HCQ	Standard care	Patients with COVID 19	Laboratory detection of viral load	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49317
ChiCTR2000029559	Randomized controlled	HCQ	Placebo	Patients with COVID 19	Laboratory detection of viral load	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=48880
NCT04304053	Randomized controlled	HCQ + Darunavir	Standard care	Close contacts with COVID 19 patients	Incidence of COVID 19 in close contacts	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04304053
ChiCTR2000029542	Randomized controlled	CQ	Standard care	Patients with COVID 19	Mortality rate; length of ICU stay; length of hospital stay	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=48968

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04321278	Randomized controlled	HCQ	HCQ + Azithromycin	Patients with suspected or confirmed COVID 19	Mortality rate; clinical status; length of hospital stay; # of days without mechanical ventilation	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04321278
NCT04303299	Randomized controlled	Oseltamivir + CQ	Different schemes of Oseltamivir, Darinavir, Lopinavir & Favipiravir	Patients with COVID 19	Detection of viral load; Mortality; length of mechanical ventilation	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04303299
NCT04322123	Randomized controlled	HCQ	HCQ + Azithromycin	Patients with suspected or confirmed COVID 19	Mortality rate; clinical status; length of hospital stay; proportion of patients intubated	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04322123
NCT04324463	Randomized controlled	CQ + Azithromycin	Standard care	Patients with COVID 19	Length of hospital stay; mechanical ventilation or death	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04324463
NCT04322396	Randomized Controlled	HCQ + Azithromycin	Placebo	Patients with COVID 19	Clinical status; Mortality; length of hospital stay	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04322396
NCT04323527	Randomized Controlled	CQ (high dosage)	CQ (low dosage)	Patients with COVID 19	Mortality rate; length of hospital stay; length of ventilator	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04323527

Appendix E. Macrolide Studies for COVID 19: Azithromycin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Gautret P, et al.	Non randomized, open label	HCQ	HCQ + Azithromycin	Patients with Confirmed COVID-19	Viral load in NPS, (+) & (-) virus at D6 post inclusion	HCQ reduced viral load & its effect is reinforced by Azithromycin.	Completed	https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub
Gautret P, et al.	Observation-al	HCQ + Azithromycin	NA	2 groups: - upper respiratory tract infection - lower respiratory tract infections	Clinical course w/ O2 support for 3 days; contagious-ness assessed by PCR/culture; length of stay	Majority had favorable outcome; early resolution of culture result; decreased length of stay (4.6 days)	Completed	https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf
Molina JM, et al.	Case series	HCQ + Azithromycin	None	COVID 19 patients hospitalized	NPS w/ qualitative PCR assay	HCQ & Azithromycin: no evidence of antiviral activity or clinical benefit in severe COVID-19	Completed	https://www.sciencedirect.com/science/article/pii/S0399077X20300858?via%3Dihub

Appendix F. IL-6 Inhibitors Studies for COVID 19: Tocilizumab, Silfuximab and Sarilumab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04320615	Randomized, double-blind, phase III	Tocilizumab	Placebo	COVID-19 Pneumonia	Clinical status using a 7-Category Ordinal Scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04320615

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Xu et al.	Observation-al	Tocilizumab + Lopinavir + Methylpred-nisolone	NA	Severe or critical COVID-19	Normaliza-tion of body temperature, O2 sat & improvement in CT scan findings	After day 1 of Tocilizumab: Normalization of temperature, improved SpO_2 & resolution of opacities on CT scan	Completed	http://chinaxiv.org/abs/202003.00026.
NCT04317092	observational cohort, phase II, parallel assignment	Tocilizumab	None	COVID-19 Pneumonia any age	One-month mortality rate	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04317092
NCT04306705	Retrospective cohort	Tocilizumab	Continuous renal replacement therapy, standard care	Severe COVID-19 pneumonia with CRS 18-80 y/o	Normalization of Fever, O2 saturation within 14 days of treatment	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04306705
NCT04331795	Non-randomized, open-label single group assignment	Tocilizumab	Tocilizumab 80 mg	Hospitalized, non-critically ill patients with COVID-19 pneumo-nitis w/o risk factors for decompensa-tion	Normalization of fever & CRP rate	NA	Recruiting	https://clinicaltrials.gov/show/NCT04331795
ChiCTR2000029765	Randomized Controlled	Tocilizumab	Standard care	COVID-19 pneumonia with elevated IL-6	Cure rate	None	Recruiting	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029765

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04315480	Single-arm Simon's 2 stages optimal design open Label phase II	Tocilizumab	None	COVID Pneumonia 18-80 y/o	Arrest in deterioration of pulmonary function, improving pulmonary function	NA	Not yet recruiting	https://ClinicalTrials.gov/show/NCT04315480
NCT04310228	Randomized controlled	Favipiravir + Tocilizumab	Favipiravir monotherapy, Tocilizumab monotherapy	COVID-19 Pneumonia 18-65 y/o	Clinical cure rate	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04310228
ChiCTR2000030894	Randomized controlled	Favipiravir +Tocilizumab	Favipiravir monotherapy, Tocilizumab monotherapy	COVID-19 pneumonia	Clinical cure rate	NA	Recruiting	http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000030894
NCT04332913	Observation-al, cohort prospective	Tocilizumab	NA	COVID-19 pneumonia >18 y/o	Fever and SpO2 normalization	NA	Recruiting	https://clinicaltrials.gov/show/NCT04332913
ChiCTR2000030196	Interventional single arm phase II	Tocilizumab	None	COVID-19 with CRS	Relief of CRS	NA	Pending	http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000030196
NCT04333914	Randomized controlled, phase II	CQ analog, Nivolumab, Tocilizumab	Standard care	COVID-19, advanced or metastatic hematologi-cal or solid tumor	28-day survival rate	NA	Recruiting	https://clinicaltrials.gov/show/NCT04333914
NCT04315298	Randomized, controlled, phase II/III	Sarilumab	Placebo	COVID-19 >18 yo	CRP change, time to improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04315298

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04331808	Randomized controlled, phase II	Tocilizumab	Standard care	COVID pneumopathy >18 y/o	Survival w/o needs of ventilator at D14, WHO progression scale <=5 at D4	NA	Not yet recruiting	https://clinicaltrials.gov/show/NCT04331808
NCT04335305	Randomized, controlled, open label phase II	Tocilizumab + Pembrolizu-mab	Standard care	COVID 19 w/ mild acute respiratory syndrome non-responsive to frontline therapy	% of patients with normalization of SpO2 ≥96%	NA	Not yet recruiting	https://clinicaltrials.gov/show/NCT04335305
NCT04335071	Randomized, controlled, phase II parallel assignment	Tocilizumab	Placebo	Patients with COVID 19	# of patients with ICU admission, intubation, death	NA	Not yet recruiting	https://clinicaltrials.gov/show/NCT04335071
NCT04322188	Observation-al, case control	Siltuximab	NA	COVID 19 w/ severe acute respiratory syndrome	Reduction of need for invasive ventilation, 30-day mortality	Interim data: 76% reduced CRP on D5, 33% reduced need for ventilation, 43% no clinically relevant change, 24% worsening & required intubation	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04322188
NCT04322773	Randomized open label phase II	Sarilumab, Tocilizumab	Standard care	COVID-19 >18 yo	Time to independ-ence from O2 therapy	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04322773

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04324073	Randomized Clinical trial, Bayesian open label, phase II/III	Sarilumab	Standard care	COVID-19 >18 yo	Survival w/o need of ventilator at D14; WHO progression scale \<5 at D4	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324073
NCT04327388	Randomized double-blind, phase II/III	Sarilumab	Placebo	COVID-19 >18 yo	Time to resolution of fever for 48 hrs or until discharge; % of patients reporting severity rating on 7-point ordinal scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04327388

Appendix G. IL1 Inhibitors Studies for COVID 19: Anakinra, Siltuximab, Tocilizumab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04339712	Non-randomized, open-label, phase II, factorial assignment (Greece)	Anakinra for macrophage activation syndrome; Tocilizumab for immune dysregulation	NA	COVID-19 patients ≥18 y/o	Change of baseline total sequential organ failure assessment score; improvement of lung function, increase of pO2/FiO2 ratio	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04339712?term=Anakinra&cond=COVID-19&draw=2&rank=2

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04330638	Randomized, Prospective interventional open label, phase III, factorial assignment (Belgium)	Anakinra + Siltuximab; Anakinra + Siltuximab + Tocilizumab; Anakinra + Tocilizumab	Standard care	Patients with COVID 19 8 to 80 y/o	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330638?term=anakinra&cond=COVID-19&draw=2&rank=2
NCT04324021	Randomized, open label, phase II/III, parallel assignment, 3 arm multicenter (Italy)	Emapalumab + Anakinra	Standard care	Patients with COVID 19 between 30 and 80 y/o	Proportion of patients not requiring invasive mechanical ventilation or extra corporeal membrane oxygenation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324021?term=anakinra&cond=COVID-19&draw=2&rank=1
NCT04341584	Randomized, open-label, phase II, parallel assignment (France)	Anakinra	Standard care	Patients with moderate, severe or critical COVID 19 pneumonia ≥ 18 y/o	Survival w/o ventilator at D14; WHO progression scale ≤ 5; cumulative incidence of successful extubation or withdrawal of NIV/high flow at D14, decrease in WHO progression scale score	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341584?term=Anakinra&cond=COVID-19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT02735707	Randomized, embedded, multifactorial, adaptive platform trial, international collaboration	Interferon-β1a + Anakinra	None	Patients with severe COVID 19 ≥18 y/o	All-cause mortality; days alive; outside of ICU	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT02735707?term=anakinra&cond=COVID-19&draw=2&rank=3

Appendix H. TNF Inhibitor Studies for COVID: Adalimumab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000030089	Randomized controlled, open-label, phase IV	Adalimumab	Standard care	Severe & critical COVID 19	Time to clinical improvement	NA	Not yet recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49889

Appendix I. Interferon (IFN) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000031196	Non-randomized controlled	Lopinavir/ ritonavir + interferon α	Standard care	RT-PCR SARS-CoV-2 (+)	Time of SARS-CoV-2 clearance	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=51112
NCT04293887	Randomized, open label, blank-controlled, multistage	rh IFN α1β 10ug bid nebulization inhalation	Standard care	Patients with COVID-19 within 7 days onset of symptoms >18 y/o	Incidence of side effects within 14 days of enrollment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04293887
NCT04276688	Randomized controlled, open-label, prospective	LPV/r + Ribavirin + IFN β-1B	LPV/r	Hospitalized Patients with COVID 19 ≥18 y/o	Time to negative NPS for SARS-Cov-2 viral RT-PCR	NA	Completed recruitment	https://clinicaltrials.gov/ct2/show/NCT04276688?cond=interferon+in+covid-19&draw=2&rank=11

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04344600	Randomized controlled, single-blind, prospective	Peg-IFN ʎ1a	Placebo	Non-hospitalized patients high risk for COVID 19 18-80 y/o	No COVID 19 at or before D28; Resolution of COVID 19 URTI	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04344600?cond=interferon+in+covid-19&draw=2&rank=10
NCT04350281	Randomized controlled, open-label, prospective	Interferon β-1b + HCQ	HCQ	Hospitalized patients with COVID 19 >18 y/o	Time to negative NPS SARS-CoV-2 viral RT-PCR	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350281?cond=interferon+in+covid-19&draw=2&rank=9
NCT04320238	Non-randomized; open label	Low risk: rh IFN α-1b 2-3 High risk: Rh IFN α-1b 2-3 + thymosin α1	None	Formally serving medical staff in Taipei Hospital 18-65 y/o	New-onset COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04320238?cond=interferon+in+covid-19&draw=2&rank=8
NCT04254874	Randomized controlled cohort, open label, prospective/ retrospective	Arbidol + Peg-IFN α-2b	Arbidol	Patients with COVID 19 pneumonia ≥18 y/0	Rate of disease remission; Time for lung recovery	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04254874?cond=interferon+in+covid-19&draw=2&rank=4
NCT04343976	Randomized, prospective, two-stage trial	Peg-IFN ʎ	Standard care	≥18 y/o with: - COVID-19 - no or early symptoms	Negative COVID PCR testing D7 days of treatment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04343976?cond=interferon+in+covid-19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04350671	Randomized, double-blind, placebo-controlled	IFN β1a plus LPV/r plus HCQ	LPV/r plus HCQ	≥ 50 y/o with COVID-19 by RT-PCR or CT Scan	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350671?cond=interferon+in+covid-19&draw=2&rank=2
NCT04343768	Randomized, open label	HCQ plus LPV/r plus IFN-β 1a	HCQ plus LPV/r	≥ 18 with COVID-19 by RT-PCR or CT Scan	Time to clinical improvement.	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04343768?cond=interferon+in+covid-19&draw=2&rank=1
NCT04350684	Randomized, double-blind, placebo-controlled	Umifenovir + IFN-β1a + LPV/r + HCQ	IFN-β1a + LPV/r + HCQ	≥18 y/o with COVID-19 by RT-PCR or CT Scan	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350684?cond=interferon+in+covid-19&draw=2&rank=6
NCT04324021	Randomized, open label, phase II/III Parallel assignment, 3-arm, multicenter study	Anti-IFN γ + Anakinra	Standard care	Hospitalized 30 to 79 y/o with COVID 19, respiratory distress & hyperinflam-mation state	Proportion of patients not requiring invasive mechanical ventilation or ECMO	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324021?cond=interferon+in+covid-19&draw=2&rank=7
NCT04254874	Randomized Controlled cohort, open label, prospective/ retrospective	Abidol + HCQ + Peg-IFN α-2b	Standard care + Abidol	≥18 y/o with COVID 19 by RT-PCR or CT Scan	Rate of disease remission; Time for lung recovery	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04254874?cond=interferon+in+covid-19&draw=2&rank=4

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04343976	Randomized, prospective, two-stage	PegIFN ʌ	Standard care	≥18 y/o with - COVID-19 - no or early symptoms	Negative COVID PCR testing 7 days after treatment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04343976?cond=interferon+in+covid-19&draw=2&rank=3

Appendix J1. Antiviral Agent Studies for COVID: Arbidol

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04286503	Randomized controlled, open label, multicentered	Carrimycin, Carrimycin with standard care	LPV/r, Arbidol, Chloroquine	COVID 19 patients 18-75 y/o	Fever to pulmonary inflammation resolution time, (-) sero-conversion	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04286503?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=4
NCT04260594	Randomized controlled, multicentered	Arbidol	Standard care	COVID 19 patients 18 – 75 y/o and above	Virus negative conversion rate in the first week	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04260594?term=Arbidol&cond=Covid+19&draw=2&rank=2
NCT04273763	Randomized, open label, sequential assignment	Arbidol, Bromhexine, IFN α2b	Arbidol IFN α2b	COVID 19 patients 18 – 80 y/o	Time to clinical recovery after treatment, rate of aggravation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04273763?term=Arbidol&cond=Covid+19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04323345	Randomized controlled, multicentered	Natural honey + LPV/r; Arbidol; HCQ + Oseltamivir + Azithromycin	Standard care	COVID 19 patients 5 – 75 y/o	Recovery rate to (-) swabs, normal temperature & resolution of lung inflammation in CT or chest X ray	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04323345?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=13
NCT04261907	Randomized controlled, open label, multicentered	ASC09/ Ritonavir, LPV/r	LPV/r	COVID 19 patients ≥18 y/o	Incidence of composite adverse outcome	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04261907?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=10

Appendix J2. Antiviral Agent Clinical Trials: Favipiravir

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04333589	Randomized controlled, open label, multicentered	Favipiravir	CQ, HCQ, Arbidol, Colomycin	COVID 19 patients 18 – 80 y/o	Viral nucleic acid test negative conversion rate	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04333589?term=Arbidol&cond=Covid+19&draw=2&rank=7
NCT04336904	Randomized controlled, double blind	Favipiravir	Placebo	COVID 19 patients 18 – 75 y/o	Time from randomiza-tion to clinical recovery	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04336904?term=Favipiravir&cond=COVID+19&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04303299	Randomized controlled, open label	Various combination of: -Oseltamivir, -Favipiravir, -HCQ -protease inhibitors	Standard care; conventional quarantine	COVID 19 patients 16-100 y/o	NPS SARS-CoV-2 eradication time	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04303299?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=20
NCT04310228	Randomized controlled, open label	Favipiravir + Tocilizumab	Faviripavir, Tocilizumab	COVID 19 patients 18-65 y/o	Clinical cure rate	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04310228?term=Favipiravir&cond=COVID+19&draw=2&rank=3
NCT04333589	Randomized controlled, open label	Favipiravir	Standard care	COVID 19 patients 18 – 80 y/o	Viral nucleic acid test negative conversion rate	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04333589?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=21

Appendix J3. Antiviral Agent Studies for COVID 19: Lopiravir/Ritonavir (LPV/r)

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04307693	Randomized controlled, open label, multicentered	LPV/r	HCQ	COVID 19 patients 16 – 99 y/o	Viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04330690	Randomized controlled, open label, multicentered	LPV/r	Standard care	COVID 19 patients ≥ 6mo old	Efficacy of intervention	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330690?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=2
NCT04286503	Randomized controlled, open label, multicentered	Carrimycin, Carrimycin with basic treatment	LPV/r, Arbidol, Chloroquine	COVID 19 patients 18-75 y/o	Fever to resolution of pulmonary inflammation, (-) sero-conversion	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04286503?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=4
NCT04321174	Randomized controlled	LPV/r	Standard care	COVID 19 ≥18 months	Microbiologic evidence of infection	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04321174?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=5
NCT04331470	Randomized Controlled, double blind	Levamisole + Budesonide + Formoterol inhaler, LPV/r + HCQ	Standard care, LPV/r + HCQ	COVID 19 patients 15 – 100 y/o	Clear chest CT scan PCR test	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04331470?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=6

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04255017	Randomized controlled	LPV/r, Arbidol, Oseltamivir	Standard care	COVID 19 patients ≥18y/o	Rate of disease remission Time for lung recovery	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04255017?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=7
NCT04295551	Randomized controlled, open label, multicentered	LPV/r + Xiyanping injection + Interferon α nebulization	Standard care	COVID 19 patients ≥18y/o	Clinical recovery time	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04295551?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=8
NCT04328012	Randomized controlled, double blind, multicentered	LPV/r, HCQ, Losartan	Placebo	COVID 19 patients ≥18y/o	Difference in NIAID COVID-19 Ordinal Severity Scale scores between the different treatment groups	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04328012?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=9
NCT04261907	Randomized controlled, open label, multicentered	ASC09/ Ritonavir, LPV/r	LPV/r	COVID 19 patients ≥18y/o	Incidence of composite adverse outcome	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04261907?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=10

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04321993	Non-randomized, open label, phase II, parallel assignment	LPV/r; HCQ; Baricitinib; Sarilumab	Standard care	COVID 19 patients ≥18y/o	Clinical status of subject at day 15	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04321993?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=11
NCT04315948	Randomized controlled, open label, multicentered	LPV/r, Remdesivir, IFN-ß-1a, HCQ	Standard care	COVID 19 patients ≥18y/o	% of subjects reporting severity rating on a 7-point ordinal scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04315948?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=12
NCT04275388	Randomized controlled, open label	Xiyanping injection + LPV/r + IFN α neb	LPV/r + IFN a neb	COVID 19 patients 18 – 70 y/o	Clinical recovery time	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04275388?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=14
NCT04251871	Randomized controlled, open label	Traditional Chinese Medicine + LPV/r + IFN α neb	LPV/r + IFN α neb	COVID 19 patients 14 – 80 y/o	Time to complete remission of COVID 19 symptoms	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04251871?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=15

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04276688	Randomized controlled, open label	LPV/r, Ribavirin, IFN β	LPV/r	COVID 19 patients ≥18y/o	Time to (-) naso-pharyngeal swab	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04276688?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=17
NCT04329650	Randomizedcontrolled, open label	LPV/r, Siltuximab, Methylpred-nisolone	Siltuximab, Methylpred-nisolone	COVID 19 patients ≥18 y/o	Proportion of patients requiring ICU admission at any time within the study period.	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04329650?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=18
NCT04328480	Randomized controlled	LPV/r	Standard care plus colchicine	COVID 19 patients ≥18y/o	All-cause mortality	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04328480?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=19
NCT04307693	Randomized controlled, open label, multicentered	LPV/r	HCQ	COVID 19 patients 16 – 99 y/o	Viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04330690	Randomized controlled, open label, multicentered	LPV/r	Standard care	COVID 19 patients ≥ 6mo old	Efficacy of intervention	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330690?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=2
NCT04328285	Randomized controlled, double blind	LPV/r	Placebo	Healthcare worker	Occurrence of an asymptoma-tic or symptomatic COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04328285?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=3

Appendix J4. Antiviral Agent Studies for COVID 19: Remdesivir

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04292899	Randomized controlled, open label	Remdesivir	Standard care	COVID 19 patients ≥ 12y/o	Odds of ratio for Improvement on a 7-point Ordinal Scale on D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04292899?term=Remdesivir&cond=COVID+19&draw=2&rank=1
NCT04292730	Randomized controlled, open label	Remdesivir	Standard care	COVID 19 patients ≥12 y/o	Proportion of participants discharged by D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/results/NCT04292730?term=Remdesivir&cond=COVID+19&draw=2&rank=2

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04252664	Randomized controlled, double blind	Remdesivir	Placebo	COVID 19 patients ≥18 y/o	Time to clinical recovery	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04252664?term=Remdesivir&cond=COVID+19&draw=2&rank=3
NCT04257656	Randomized Controlled, double blind	Remdesivir	Placebo	COVID 19 patients ≥18 y/o	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04257656?term=Remdesivir&cond=COVID+19&draw=2&rank=5
NCT04321616	Randomized controlled, open label	HCQ + Remdesivir	Standard care	COVID 19 patients ≥18 y/o	In-hospital mortality	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04321616?term=Remdesivir&cond=COVID+19&draw=2&rank=6
NCT04280705	Randomized controlled, double blind	Remdesivir	Placebo	COVID 19 patients 18 – 99 y/o	% of subjects reporting severity rating on an 8-point ordinal scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04280705?term=Remdesivir&cond=COVID+19&draw=2&rank=7

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04315948	Randomized controlled, open label	LPV/r + Remdesivir + IFN-ß-1a + HCQ	Standard care	COVID 19 patients ≥18 y/o	% of subjects reporting severity rating on a 7-point ordinal scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04315948?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=12

Appendix J5. Antiviral Agent Study for COVID 19: Ribavirin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04276688	Randomized, open label	LPV/r + Ribavirin + IFN β	LPV/r	COVID 19 patients ≥18 y/o	Time to negative naso-pharyngeal swab	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04276688?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=17

Appendix K. JAK Inhibitor Studies for COVID: Baricitinib

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04340232	Interventional open label, phase II/III, single group assignment	Baricitinib	Standard care	Patients with COVID 19	COVID 19 progression, blood test results, incidence of adverse events	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04340232?term=Baricitinib+for+COVID&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04320277	Non-randomized, open label, phase III, crossover	Baricitinib + Ritonavir	Antiviral and/or HCQ	Mild to moderate COVID 19 ≥18 yrs	Statistical difference of % of ICU admission between patients and controls	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04320277?term=baricitinib&draw=3&rank=14
NCT04321993	Non-randomized, open label, phase II, parallel assignment	Baricitinib	HCQ + LPV/r; HCQ + Imatinib	Hospitalized moderate to severe COVID 19 ≥18 y/o	Clinical status of subject at day 15 (on a 7-point ordinal scale)	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04321993?term=baricitinib&draw=1&rank=62

Appendix L. CCR5 Inhibitor Studies for COVID 19: Leronlimab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04343651	Randomized controlled, double blind, phase II, parallel assignment	Leronlimab	Placebo	Mild to moderate COVID 19 with respiratory disease ≥18 y/o	Clinical improvement as assessed by symptom scores	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04343651?term=leronlimab&cond=covid+19&draw=2&rank=1

Appendix M. Mesenchymal Stem Cells (MSC) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04315987	Non-randomized, open label, single group assignment	MSCs	None	Severe COVID 19 Pneumonia	Disappear time of ground-glass shadow in lungs	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04315987?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=1

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04313322	Open label, single group assignment	WJ-MSCs	NA	Patients with COVID 19	Improvement of clinical symptoms, CT scan & rT-PCR results	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04313322?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=2
NCT04288102	Randomized controlled, double-blind, quadruple masking	MSCs	Placebo	COVID 19 patients with severe Convales-cence	Size of lesion area, severity of pulmonary fibrosis (chest CT), evaluation of pneumonia improvement	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04288102?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=3
NCT04336254	Randomized, triple masking, parallel assignment, prospective	Allogeneic human dental pulp stem cells	Placebo	Severe COVID 19 Pneumonia	Time to Clinical Improvement	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04336254?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=4
NCT04273646	Randomized; open label, partial assignment	UC-MSCs	Placebo	Severe COVID 19 disease	Evaluation of pneumonia improvement	NA	not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04273646?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=5

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04339660	Randomized, triple masking, partial assignment	UC-MSCs	Placebo	COVID 19 Pneumonia	Improvement & recovery time of inflammatory & immune factors; blood oxygen saturation	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04339660?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=6
NCT04302519	Open label, single group assignment	Dental pulp mesenchy-mal stem cells	NA	Severe COVID 19 pneumonia	Disappear time of ground-glass shadow in lungs	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04302519?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=7
NCT04252118	Non-randomized, open label, parallel assignment	MSCs	None	COVID 19 Pneumonia	Size of lesion area by chest radiograph or CT, side effects of MSC	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04252118?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=8
NCT04345601	Pilot study, open label, single group assignment	MSCs.	NA	COVID 19 induced acute respiratory failure	Adverse reactions, improved oxygen saturations ≥93%	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04345601?term=mesenchymal+stem+cells&cond=COVID&draw=2&rank=10

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04269525	Open label, single group assignment	UC-MSCs	NA	Serious and critical COVID Pneumonia	Oxygenation index	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04269525?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=11
NCT04333368	Randomized, triple masking, parallel assignment	Umbilical cord Wharton's jelly-derived human MSC	Placebo	COVID 19 related ARDS	Respiratory efficacy evaluated by the increase in PaO2/FiO2 ratio from baseline to day 7	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04333368?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=12
NCT04341610	Randomized controlled, double-blind, quadruple masking, parallel assignment	Allogeneic adipose-derived mesenchy-mal stromal cells	Placebo	Severe COVID 19 respiratory disease	Changes in clinical critical treatment index	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04341610?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=14
NCT04276987	Open label, single group assignment	MSCs-derived exosomes	NA	Patients with severe COVID 19 Pneumonia	Adverse reaction & severe adverse reaction	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04276987?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=15

Appendix N. Vitamin C Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04323514	Uncontrolled longitudinal, open label, single group assignment	Vit C	NA	All ages with indication of intubation, (+) swab test for COVID 19	Change of mortality	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04323514
NCT04264533	Randomized, triple masking, phase II, parallel assignment	Vit C	Placebo	COVID 19 in ICU ≥18 y/o	Ventilation free days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04264533
NCT03680274	Randomized, quadruple masking, phase III, parallel assignment	Vit C	Placebo	COVID 19 in ICU ≥18 y/o	Deceased participants or persistent organ dysfunction	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT03680274

Appendix O. Availability of the immunomodulators in the Philippines

FDA approved	Solidarity trial (COVID 19)	Not available
Adalimumab (RA) Globo 889-827-000	Convalescence plasma	Anakinra (RA)
Ascorbic acid (scurvy, dietary supplement)	Hydroxychloroquin, Chloroquin	Arbidol
BCG (routine NB vaccine for TB)	Lopiravir/Ritonavir	Baricitinib
Corticosteroid: Methylprednisolone, prednisone, prednisolone, dexamethasone (inflammatory diseases)	Interferon β 1a	Favipabir
Hydroxychloroquin, Chloroquin (Malarial disease, SLE, RA)	Remdisivir	Leronnimab
Interferon α, β, γ, α 2A, α 2B, β 1a, β 1b (MS, viral hepatitis, CGD)		
IVIG (KD, PID)		
Lopinavir/Ritonavir (HIV infection)		
Mesenchymal stem cell (Musculoskeletal diseases, MS, cancer)		
Peginterferon α 2a (anti-viral, cancer immunotherapy)		
Ribavirin (RSV, Hepatitis C, HIV)		
Tocilizumab (RA) Globo 889-827-000		
Zinc sulfate (AGE, dietary supplement)		