Philippine Society of Allergy, Asthma and Immunology, Inc.

A REVIEW OF IMMUNOMODULATORS AS THERAPEUTIC INTERVENTIONS FOR MODERATE TO SEVERE COVID-19 INFECTIONS (Version 2.0, May 10, 2020)

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A REVIEW OF IMMUNOMODULATORS AS THERAPEUTIC INTERVENTIONS FOR MODERATE TO SEVERE COVID-19 INFECTIONS
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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.

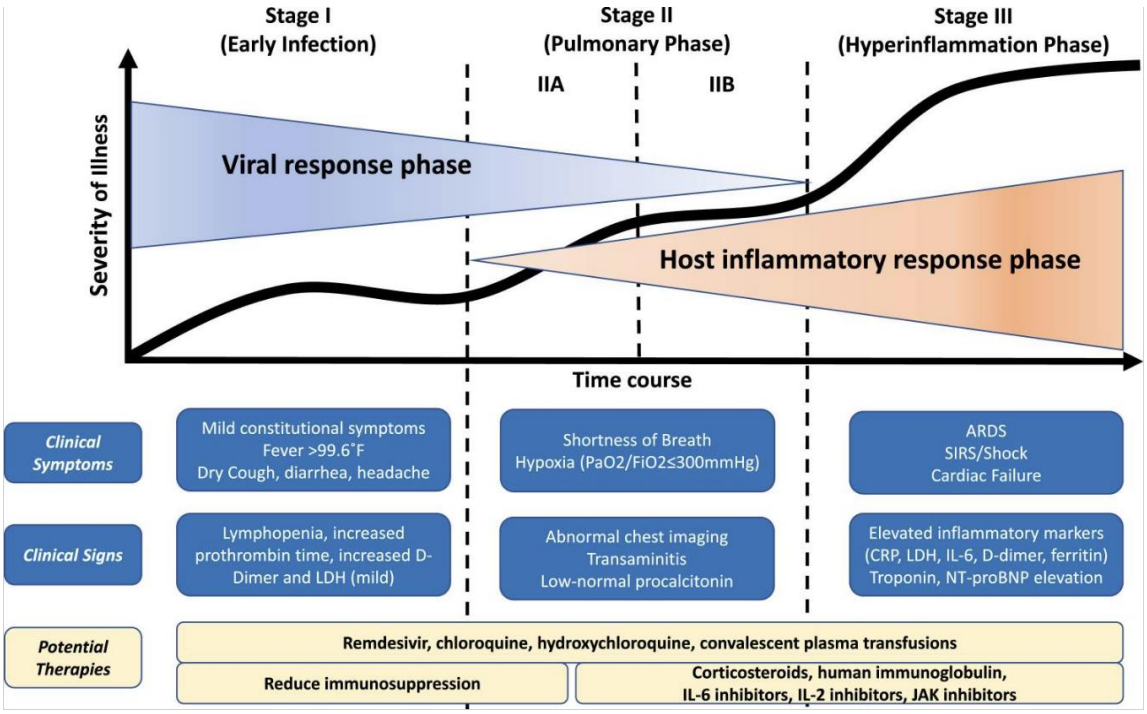

Figure 1. Classification of COVID-19 Disease States and Potential Therapeutic Targets
The figure shows 3 escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome, CRP=C-reactive protein; 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.

Another clinical complication of the cytokine storm is the development of coagulopathy in a COVID patient with ARDS. The hypercoagulable state in patients with severe COVID disease may be due to several mechanisms: disruption of endothelial function due to imbalances in angiopoetin-1 and 2 and activation of plasminogen which lead to fibrinolysis and complement-mediated microvascular lung injury[9,10.] Therefore, low fibrinogen levels, with decreasing ESR, in the setting of rising CRP levels is commonly seen in CRS. All these findings may actually herald the onset of disseminated intravascular coagulation which is a very important determinant for multiple organ failure. [9]

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.[11] 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.[11] 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.[12] 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:[13]

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.

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IMMUNOMODULATORS FOR COVID-19

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. Azithromycin
   4. Targeted Monoclonal antibodies (Cytokine Antagonists)
      a. Anti-IL-6 (tocilizumab, siltuximab, sarilumab)
      b. Anti-IL-1 (anakinra, rilonacept, canakinumab)
      c. IL-2 (aldesleukin)
      d. Anti-TNF (adalimumab)
      e. Anti-GM-CSF (lenzilumab)
      f. JAK-1 inhibitors (baricitinib, ruloxitinib)
      g. CCR-5 inhibitor (leronlimab)
   5. IFN and IFN Inhibitors
   6. Calcineurin Inhibitors (cyclosporine, tacrolimus)
   7. Anti-viral agents (lopiravir/ritonavir, ribavirin, umifenovir, remdesivir, favipiravir, oseltamivir)
   8. Aspirin
   9. Azathioprine
   10. Colchicine
   11. ACE Inhibitors and Angiotensin receptor blockers
   12. Statins
   13. Alpha-receptor antagonists
   14. Stem cell therapy
   15. BCG vaccine
   16. Inosine pranobex
   17. Alpha-reactive antibodies
   18. Supplements
      a. Vitamin C
      b. Vitamin D
      c. Zinc
      d. Melatonin
      e. Quercetin
      f. Probiotics
      g. DHA/Omega 3 fatty acids

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]

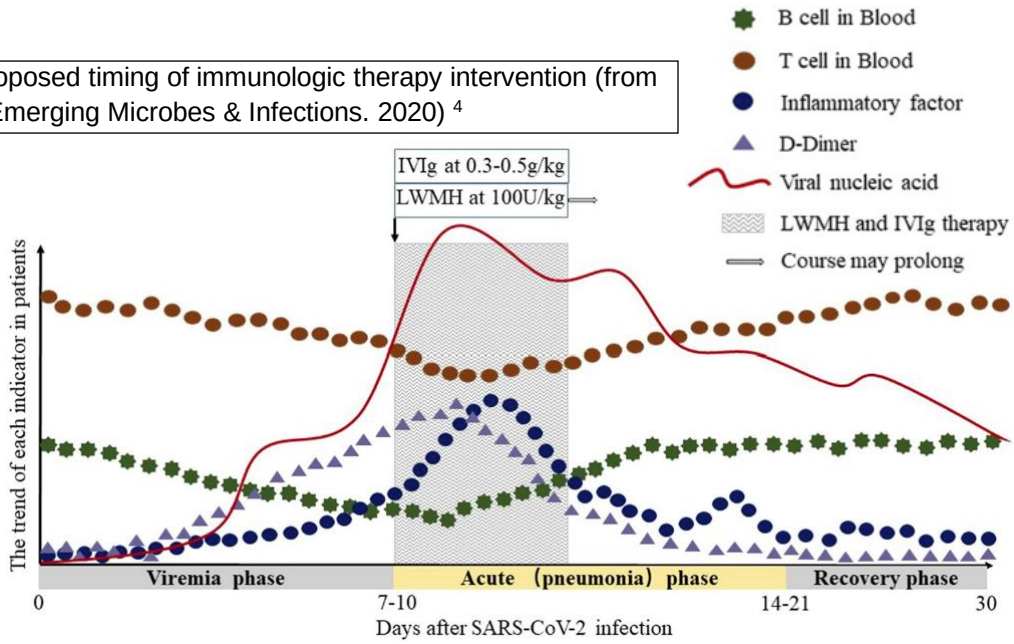
Mechanism of action and effect on COVID-19 infection

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] and inhibit the formation of cytokine storm.[5] 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 1)

There is limited evidence of IVIG for COVID-19. 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 reports and case series).[6,7,8,9,10] 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).[11] Another retrospective study showed significant reduction in 28-day mortality, ventilator use, hospital and ICU length of stay.[12] A prospective cohort study by Zhou et al. involving 10 COVID-19 patients showed improvement after giving moderate-dose corticosteroid and IVIG treatment.[13] 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.[14]

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.[14]

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.[15] 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.[15] 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.[16-17]

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. 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.

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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] In COVID-19, the S1 portion of the spike protein in COVID-19 has been characterized and at this time, it is known to allow viral attachment via the ACE2 receptor on the host cell which eventually allows entry into the cell.[5] Neutralizing antibodies present in the CP, specific to either the ACE2 receptor or the S1 protein is postulated to block this from happening.

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 2) 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 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 of maintain the neutralizing antibodies at high levels leading to the disapperance of viremia in 7 days.[6]

In another case series by Shen 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. [7]

Other interventional trials in several countries are currently being conducted. (Appendix 2)

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. [8,9,10]

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.[6,7]

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.[8] 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.[9]

Adverse Effects

There can be mild reactions like evanescent red spots as reported by Duan et al.[6] Other non-infectious hazards of tranfusions are allergic transfusion reactions and transfusion associated circulatory overload (TACO).[8] 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 transfusion related acute lung injury (TRALI)[11] considering its use in active treatment of individuals with pulmonary disease. The specific risk of transfusion-

transmitted SARS-CoV-2 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.[12] 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.

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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.

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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 a systematic review of observational 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 cohort 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]

By performing a review of articles, 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 Hunan, China, 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 May 10, 2020, there are 4 new ongoing trials on the use of steroids for COVID-19: 2 randomized controlled trials, one of which is recruiting participants already; 1 randomized open label trial and 1 non-randomized open label study. Both of the latter researches are likewise recruiting subjects. (Appendix 3)

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.

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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 cGAS-STING signaling which reduce the release of proinflammatory cytokines [2,6]

Efficacy and Safety Of HCQ and CQ on COVID-19

*Efficacy and Safety of HCQ or CQ **Monotherapy** for COVID-19*

As of May 10, 2020, there are 3 randomized controlled trials and 2 observational studies 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]

In an observational study of 1376 patients admitted due COVID-19, hydroxychloroquine administration was not associated with intubation or death (hazard ratio, 1.04, 95% confidence interval, 0.82 to 1.32).[10]

A parallel, double-masked randomized, phase IIb clinical trial of 81 adult patients with severe COVID-19 was stopped due to high mortality rate (39%; 16 of 41 patients) among those who received high dose CQ (600 mg CQ; 4 × 150 mg tablets twice daily for 10 days; total dose 12 g).[11]

*Efficacy of **Hydroxychloroquine and Azithromycin** for COVID-19*

There is only one open-label clinical trial[12] and 2 observational studies[13,14] 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 RNA load, however

result of the study should be interpreted with caution due to the methodologic concerns and a small sample size.[12]

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 hospitalized, probable or confirmed COVID-19 cases with moderated to severe pneumonia.[15]

Several national and society guidelines (China, Italy, Netherlands, Belgium) have included HCQ in the management of COVID-19 pneumonia.[16,17,18] 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 4 and Appendix 5)

Recommended Dose

- HCQ – 200 mg tablet
  - Adult dose[15]: 200 mg tab 2 tabs BID day 1 then 1 tab BID x 9 days
  - Pediatric Dose[19]: ≥6 years old at 5 mg/kg/day BID (Max 400 mg)
    - 6-8 y/o: Day 1: 1 tab BID; Day 2-5: ½ tab BID
    - 9-11 y/o: Day 1: 1½ tab BID; Day 2-5: ½ to 1 tab BID
    - ≥12 y/o: Day 1: 2 Tabs BID; Day 2-5: 1 tab BID
- CQ
  - Adult dose[15]: 500 mg BID x 10 days
  - Pediatric dose[19]: 10 mg (base)/kg/day BID (Max 500 mg phosphate or 300 mg base/dose). Given for a total treatment duration of 5-10 days
    - 0-11 months ½ tab BID;
    - 1-3 y/o 1 tab BID;
    - 4-6 y/o 1½ tab BID;
    - 7-11 y/o 2 tabs BID;
    - 12-15 y/o 3 tabs BID;
    - ≥16 y/o 4 tabs BID

Adverse Effects

The use of HCQ or CQ in patients with COVID-19 has been associated with QTc prolongation and torsades de pointes.[9, 20] The development of acute renal failure among those given the combination of HCQ and azithromycin was a strong predictor of severe QTc prolongation.[20] 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, 12,13]

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. HCQ and CQ have potential for toxicity and lethality for CQ when given at high doses. 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.

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3. AZITHROMYCIN

Introduction

Azithromycin is a macrolide, belonging to a class of antimicrobials with activity mainly against gram-positive cocci and atypical pathogens.[1] A body of evidence supports its broad activities as an immunomodulator especially among those with chronic inflammatory disease.

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

The evidence that has been presented on the April 20, 2020 review was based on the open-label study of 26 COVID-19 patients comparing the use of azithromycin plus hydroxycholoroquine (N=6), and hydroxychloroquine alone (n=14). Six hydroxychloroquine were lost to follow up. The combination therapy has shown significant decline in viral RNA starting on the 3rd day (*p* value= 0.002) compared to hydroxychloroquine monotherapy.[4] However, a similar study by Lane, J[8] which included 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin has documented new information regarding this matter. This study concluded that short-term hydroxychloroquine treatment is safe, but addition of azithromycin may induce heart failure and cardiovascular mortality, potentially due to their synergistic effects on QT length. A call for caution when using hydroxychloroquine and azithromycin combination is advised in the management of COVID-19 patients.

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

Conclusion

Currently, conflicting data regarding combination therapy from different studies all over the world are starting to come out. Though combination of azithromycin and hydroxychloroquine can decrease viral RNA load[4], the addition of azithromycin may potentially trigger cardiovascular complications.[8] There is no study to date that determines the effect of azithromycin alone in COVID-19.

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4. TARGETED MONOCLONAL ANTIBODIES

a. ANTI-INTERLEUKIN 6 (IL–6) or 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 FDA for the treatment of cytokine release syndrome (CRS) that is severe or life-threatening. 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 are two observational studies [7,8], 1 case report [9] and 23 registered clinical trials on the use of tocilizumab for COVID-19 patients. (Appendix 6). 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]

In a prospective open, single-arm multicenter study of 63 patients with severe COVID-19, the use of tocilizumab within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3–6.7).[8]

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.[10]

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[11] and the Italian Society of Infectious Diseases and Tropical Diseases COVID-19 Guideline[12] have recommended the use of tocilizumab as a treatment option for patients with severe COVID-19.

Recommended Dose

A. Tocilizumab:

   Adult dose:

   - 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[13]
   - 4-8 mg/kg single dose or 400mg IV diluted in 0.9 NS to 100 ml, given as a 2-hour infusion; a single extra dose may be given after 12 hours at the discretion of the provider[14]

   Pediatric dose:

   - 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[15]

B. Sarilumab: 400 mg single IV dose or 200-400 mg SC dose[16]

C. Siltuximab: 11mg/kg infused over one hour with a potential second dose at the physician's discretion[10]

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.[17] 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.

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b. ANTI-INTERLEUKIN 1 (IL–1) or 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 suppresses 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

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]

A recently published retrospective chart review reported five patients diagnosed with MAS who were given continuous IV infusion because of worsening clinical status. Four of the five patients had rapid serologic then clinical improvement.[10] Another retrospective chart review of all anakinra-treated MAS patients showed that (≤5 days hospitalization) earlier initiation of anakinra was associated with reduced mortality (p=0.046).[11] A prospective case series of nine consecutive moderate to severe COVID-19 pneumonia patients at high risk of worsening were given anakinra for 10 days. Results showed that 1 patient developed acute respiratory failure after 1 dose; the 8 other patients had good clinical and biologic outcomes.[12]

Some patients with COVID-19 progress to a third stage with cytokine storm syndrome/MAS. Based on the above studies, there are currently ten clinical trials registered in ClinicalTrials.gov using anakinra alone or in combination with other immunomodulators for COVID-19. There are now three studies using canakinumab. (Appendix 7)

Recommended Dose

In various ongoing clinical trials (Appendix 7), the following are the dose ranges were used:

Anakinra: 100 mg - 400 mg / day IV (with varying duration)
100 mg / day SC (also with varying duration)

Canakinumab: 300 mg - 600 mg / day IV (single dose); one study gave it SC (no dose and duration mentioned)

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 subcutaneous use (10 years).[1] In the study by Monteagudo et al., all 5 patients developed cytopenia with IV infusion which could be due to the known clinical course of MAS or due to the high dose anakinra; in one patient the cytopenia returned to normal after dose reduction.[10]

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 or an observational study; hence, its use for COVID-19 CSS should be in the context of a clinical research.

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c. INTERLEUKIN–2

Introduction

Interleukin-2 (IL-2) has been discovered in 1976 as a T cell growth factor. IL-2 is a key cytokine for Treg cell differentiation, survival, and function[1,2,3,4] and induction of antibody production by B cells. This has led to new opportunities for tipping the balance between Treg and effector T cells towards Tregs development.[5]

The immunological and clinical effects of low dose IL-2 have already been observed in the treatment of different autoimmune diseases such as such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriasis, Behcet's disease, granulomatosis with polyangiitis, Takayasu's disease, Crohn's disease, ulcerative colitis, autoimmune hepatitis and sclerosing cholangitis.[6]

Mechanism of Action

Aldesleukin (recombinant IL-2; rIL-2) is a non-glycosylated interleukin-2 (IL-2) product, made via recombinant DNA technology that uses an *E. coli* strain containing an analog of the human IL-2 gene[7] . The biological activity of aldesleukin is similar to that of endogenous IL-2. Aldesleukin is currently FDA-approved for treating metastatic renal cell carcinoma and melanoma.[7] In HIV-related clinical trials, aldesleukin is the most commonly studied IL-2 product.[8]

Low dose IL-2 specifically activates the T reg cells and improves inflammatory conditions arising from T reg insufficiency such as allergy and autoimmunity in mice and humans[9,10,11,12,13]. IL-2 has also been used in the field of transplantation.[9] However, given the pleiotropic effects of IL-2 on other immune cell types that also respond to IL-2 in higher doses, such as CD4 and CD8 effector T cells (Teff), natural killer cells, and group 2 innate lymphoid cells[12] and given its short half-life[14], finding a dose and schedule of administration that can maintain a proper balance of Treg/Teff cells over time is the key to the therapeutic use of low dose IL-2.[15]

Depletion of Treg cells in models of lung infection and after beryllium exposure has been observed to aggravate lung inflammation, thus the important role of Treg during early ARDS and its resolution is clear. Low dose IL-2 is the first therapy during Treg-specific expansion and activation. It was successfully tested in a wide range of preclinical models of inflammatory diseases including beryllium-induced lung inflammation. It was also observed that IL-2 is very low in concentration in the blood and bronchoalveolar lavage supernatant of patients in early phase of ARDS so additional IL-2 could be beneficial for Treg expansion. This was lifted from a manuscript that describes how IL-2 can be used as treatment for ARDS caused by COVID-19. (Appendix 8)

Clinical Studies

There is presently an ongoing interventional study in Paris, France on low dose IL-2 in acute respiratory distress syndrome related to COVID-19 patients. Thirty participants will be recruited with the aim of investigating the therapeutic benefit of low dose IL-2 as a Treg inducer for controlling SARS-CoV2 related ARDS. (Appendix 8)

Recommended Dose

No specific dose was mentioned in the study of IL-2 given to COVID-19 related ARDS. (Appendix 8)

Adverse Effects

Common adverse effects of Interleukin-2 are fever and flu-like symptoms, generalized flushing of the face and body, nausea and vomiting, lower blood pressure, diarrhea and changes in mental status. These side effects occur in more than 30% of patients, are predictable and reversible when treatment is completed. A serious, but very uncommon side effect of Interleukin-2 in high doses is "capillary leak syndrome" or "vascular leak syndrome." [16]

Conclusion

Interleukin-2 may have beneficial effects in controlling inflammatory lung disease but more studies are needed to verify its effectiveness and efficacy for COVID-19.

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d. ANTI-TNF or TNF INHIBITORS

Introduction

Tumor Necrosis Factor Alpha (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 SARSCoV 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 cellbound forms of 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 9).

Recommended Dose

Studies pertaining to the use of TNF inhibitors are very limited, and there has been no mention of its dose for COVID-19. Feldmann et al. have proposed that they should be initiated as early as is practicable.[4]

Adverse Effects

Serious adverse reactions (>0.2 events/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.[5] 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.[6]

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.[7]

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.

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e. ANTI-GM-CSF OR GM-CSF INHIBITORS

Introduction

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) is a hematopoietic growth factor. Its inflammatory activity is primarily due to its role as a growth and differentiation factor for granulocyte and macrophage populations.[1]

It is one of the key molecules involved in the cytokine storm seen among COVID-19 patients.[2]

Mechanism of Action

GM-CSF is a crucial initiator in the systemic inflammatory pathway driving the chimeric antigen receptor T cell (CAR-T) associated cytokine release syndrome (CRS).[3] It enhances proinflammatory cytokine production, antigen presentation and phagocytosis, and promotes leukocyte chemotaxis and adhesion.[4]

Overexpression of GM-CSF is associated with several human pathologies such as rheumatoid arthritis, multiple sclerosis, juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML). [5]

GM-CSF neutralization prevents CD14+CD16+ inflammatory myeloid cell activation and reduces all downstream monokine production.[6] Blockage of this growth factor may halt the immunopathology caused by the virus.[7]

Lenzilumab is a humanized monoclonal antibody (class IgG1 kappa) designed to target and neutralize GM-CSF. It is currently being evaluated as a potential treatment for JMML & CMML.[8]

Clinical Studies

There are no published studies on the efficacy and safety of GM-CSF inhibitors for the management of patients with COVID-19.

A clinical trial on Lenzilumab and another GM-CSF inhibitor, TJ003234, are currently registered for the treatment of COVID-19 infection. [9] (Appendix 10)

Recommended Dose

No dose provided

Adverse Effect

Further studies are needed to determine any adverse reactions from GM-CSF inhibitors.

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be

made on the efficacy and safety of GM-CSF inhibitor to treat COVID-19 infection.

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f. JAK 1 AND 2 INHIBITORS (BARICITINIB AND RUXOLITINIB)

Introduction

Baricitinib was licensed in 2018 for treating rheumatoid arthritis with excellent clinical response and no significant safety concerns,[1,2,3] while Ruxolitinib is FDA-approved for the treatment of myelofibrosis in 2012,[4] polycythemia vera in 2015,[5] and graft-versus-host disease in 2019.[6]

Mechanism of Action

Baricitinib and ruxolitinib are selective inhibitor of Janus kinases (Jaks) 1 and 2. Janus family of kinases comprises four members: Tyk2, Jak1, Jak2 and Jak3. They 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.[4,7,8]

Baricitinib also effectively inhibits AP2-associated protein kinase 1 (AAK1) and cyclin-G associated kinase (GAK) which mediate viral endocytosis, thereby inhibits viral entry into the host cells.[7,8]

Knowing the advantageous action of baricitinib and ruxolitinib on cytokine outbreak and additional action of baricitinib on viral entry, it has been suggested that it could be used in COVID-19 patients with acute respiratory disease. Their role would be to reduce viral entry and or aberrant inflammatory response in the patients.[9]

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.[10]

Clinical Studies

To date, no published clinical trial evidence for baricitinib and ruxolitinib as 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.[11]

Six clinical trials of baricitinib and 14 of ruxolitinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future. (Appendix 11)

Dosage

Baricitinib:

Adult dose: 2-4mg once daily for 10-14 days

Pediatric dose: Safety and efficacy not established

Ruxolitinib:

Adult dose: 10mg twice daily for 14 days

Pediatric dose ≤12 y/o: Safety and efficacy not established[12]

Adverse Effects

The majority of adverse reactions of baricitinib 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; (2) Lymphoma and other malignancies observed; (3) Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), observed at an increased incidence. Ruxolitinib, on the other hand are associated with peripheral blood cytopenia, hyperlipidemia and elevated liver enzymes. It may also cause viral as well as bacterial infections.[10]

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy and safety of baricitinib and ruxolitinib to treat COVID-19. Results and findings from the ongoing studies of baricitinib and ruxolitinib for COVID-19 will help determine whether it can be used more widely in this setting.

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g. 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 inhibitor or 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 April 28, 2020, Leronlimab (Pro 140) a CCR5 antagonist target therapy immunomodulator drug has been approved for 54 patients for eIND with the US FDA. There are 49 patients enrolled in a Phase II and Phase IIb/III randomized double blind trial[2] for mild to moderate and severely and critically ill COVID-19 patients respectively. A eIND for compassionate use was requested for the patients who did not qualify for the trials. The primary clinical end point is on day 28 and secondary endpoint is on day 14.

The preliminary results are from the 14th day clinical end point for severely and critically ill of the Phase IIb/III trials. The initial results provided are from the 39/49 patients enrolled and are awaiting the report of 10 patients . Of the 39 patients, 9 (23%) patients went home, plus 18 (46%) patients showed improvement (including extubation, weaning mechanical ventilation, decreasing need of O2), 2 (5%) remained the same, 3 (8%) patients deteriorated, and 2 (5%) have pending results. So a total 32(82%) patients are still alive, with 69% of patients reported improved or improving and 5% remained the same and 8 percent deteriorated [2]. (Appendix 12)

Recommendad Dose:

700 mg subcutaneous[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

The preliminary results of a Phase IIb/Phase III randomized double blind trial of Leronlimab for severe to critically ill COVID-19 patients seem very promising although the initial data should be interpreted with caution as the study is still ongoing. The results for Leronlimab for mild to moderately ill COVID-19 are not yet available.

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5. INTERFERON and INTERFERON INHIBITORS

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 proinflammatory 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] In a retrospective cohort study done among pediatric patients with mild to moderate COVID-19, combination interferon alfa aerolization and lopinavir-ritonavir resulted in a complete cure of all 36 patients. Improvement in pneumonia was seen 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 days of treatment and the mean number of days in hospital was 14 days.[6]

In a non-randomized retrospective study, 77 adults hospitalized with confirmed COVID-19 were treated with either nebulized IFN-α2b, arbidol, or a combination of IFN-α2b plus arbidol. Study results showed that treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced duration of elevated blood levels for the inflammatory markers IL-6 and C-reactive protein.[7] Additionally, 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.[8] Moreover, there are at least 15 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, a monoclonal antibody targeting interferon gamma (Anti-IFNγ), and Anakinra versus standard of care, in reducing hyperinflammation and respiratory distress in patients with SARS-CoV-2 Infection. These studies are either currently recruiting or not yet recruiting. Two studies have completed recruitment but there are no available results yet. Therefore, these findings suggest that IFN should be further investigated as a therapy in COVID-19 cases. (Appendix 13)

Currently in China, the Novel Coronavirus Infection Pneumonia Diagnosis and Treatment Standards (the fourth edition) and Diagnosis, treatment and prevention of 2019 novel coronavirus infection in children: experts' consensus statement listed IFN-α atomization as a choice of treatment for 2019nCoV pneumonia.[9] In adults, the COVID-19 Clinical Practice Guidelines (2020) of the Medical and Health Care Wuhan University Novel Coronavirus Management & Research Team and China International Exchange & Promotive Association for Medical and Health Care recommends IFN- alpha and lopinavir/ritonavir as the antiviral therapy.[10]

Recommended Dose

Population	Preparation	Dose
Pedia[9]	Interferon α nebulization	200,000-400,000 IU/kg or 2-4 μg/kg in 2 ml sterile water, nebulization 2x per day for 5-7 days
	Interferon –α2b spray	*Note: Applied for high risk populations with a close contact with suspected 2019-mCoV infected patients OR those in the early phase with only upper respiratory tract symptoms*
	Interferon –α2b spray	1-2 sprays on each side of the nasal cavity, 8-10 spray on the oropharynx
	Interferon –α2b injection	8000 IU, once every 1–2 h, 8–10 sprays/day for 5–7 days
Adult[11]	Interferon α	5 million units or equivalent dose in 2 ml sterile water via vapor inhalation 2x a day for no more than 10 days

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.[12]

In children, IFN-α (> 2 μg/kg/time) could cause myelosuppression. Overdose of IFN-α also could cause liver enzyme abnormalities, renal failure, bleeding. IFN-α is contraindicated in patients with abnormal liver function. In children with creatinine clearance (CrCl) below 50 mL/min, IFN-α is prohibited. IFN-α is also contraindicated in children with histories of mental illness, severe or unstable heart disease, or aplastic anemia. IFN-α nebulization should be used with caution in neonates and infants younger than 2 months. Adverse reactions of IFN-α mainly include low-grade fever and flu-like symptoms (both in children with intramuscularly injection). Growth and development inhibition is more common when combining IFN-α with ribavirin. Suicidal ideation is more common in children (mainly adolescents) compared with adults (2.4% vs. 1%). [13]

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, but more clinical trials are needed to validate this. There is insufficient evidence to conclude its efficacy and safety in the treatment of COVID-19. Use with caution in children.

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6. CALCINEURIN INHIBITORS

Introduction

Calcineurin Inhibitors (CINs) are immunosuppressants, that, alongside corticosteroids, are the standard for transplant maintenance. As a group, the CINs decrease cell-mediated immune response by suppressing Interleukin 2 (IL-2) production through their inhibition of calcineurin. [1,2]

CINs may be useful in patients with COVID-19 by their activity as immunomodulators in the treatment of hyperinflammation/cytokine storm, as well as having the potential for viral suppression.

a. CYCLOSPORINE

Introduction

Cyclosporine-A (CsA) is a fungus derived molecule discovered in 1970 and is used in high as well as low doses.[1]

High dose CsA is widely used to prevent primary rejection in solid organ transplantation. It is also indicated for preventive or curative treatment of graft-vs.-host disease (GVHD) and treatment of inflammatory disorders such as psoriasis, atopic dermatitis, nephrotic syndromes, or rheumatoid arthritis. Low dose CsA has been used for immunomodulation, graft vs. host disease (GVHD) and cancer therapy.[1]

Mechanism of Action

In high doses CsA binds with cyclophilins, forming a drug-receptor complex which competitively binds to calcineurin decreasing the transcription of Interleukin 2 (IL2) and several immunologically important factors including IL-3, IL-4, tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ). In low doses a paradoxical immunomodulation occurs, increased auto-immunity and anti-cancer immunity.[1]

In vitro studies show the potential to inhibit viral growth and replication of SARS-CoV1 and MERS-CoV in low non-cytotoxic doses.[3]

Cyclosporine has been used to treat cytokine storm related syndromes in Juvenile Rheumatoid Arthritis (JRA), hematologic disorders and Systemic Lupus Erythematosus (SLE).[4,5,6,7]

Clinical Studies

A case study of a renal transplant patient on Cyclosporine who survived COVID-19 adds to the possibility of its use as therapy, although no conclusions can be derived from a single case.[8] While a few articles have proposed that CINs may have a role in the treatment of COVID-19,[1,9] there are no ongoing clinical studies using Cyclosporine for COVID-19. (Appendix 14)

Recommended Dose

Still to be established but a low, non-cytotoxic dose: ≤ 3 mg/kg, may be preferred to high Dose: ≥ 4-5mg/kg/dose[1]

Adverse Effects

The principal adverse reactions to cyclosporine therapy are nephrotoxicity and hypertension. Tremors, hirsutism, hyperlipidemia, and gum hyperplasia also are frequently encountered. Hypertension occurs in about 50% of renal transplant and almost all cardiac transplant patients. Hyperuricemia may lead to worsening of gout, increased P-glycoprotein activity, and hypercholesterolemia. [2]

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b. TACROLIMUS

Introduction

Tacrolimus (FK506) is an immunosuppressive drug discovered in 1984, chemically known as a macrolide. Its main use is in the prevention of primary rejection in solid organ transplant. It inhibits T-lymphocyte signal transduction in a similar mechanism as Cyclosporin.[1,2]

Mechanism of Action

Tacrolimus binds to the immunophilin FKBP-12 (FK506 binding protein) creating a complex that inhibits T-lymphocyte signal transduction and IL-2 transcription. Inhibition of other cells also occur and there is evidence for its use in immunomodulation in cytokine storm syndromes. Authors draw a parallel between the excessive pro-inflammatory cytokine release in conditions like hemophagocytic lymphohistiocytosis (HLH)[3] and Macrophage Activation Syndrome (MAS)[4] with COVID-19 and propose the possible use of Tacrolimus in the later.

In vitro studies shows that Tacrolimus inhibits viral growth and replication for coronavirus.[5,6]

Clinical Studies

In a case report of COVID-19 in 7 kidney transplant patients, the authors draw no conclusion on the immunomodulatory effect of Tacrolimus maintenance on outcomes.[7] Another case report on COVID-19 in 3 long term liver transplant patients (one on Tacrolimus) can draw no conclusion.[8] However, both authors voice out the need for evidence regarding Tacrolimus' effect on cytokine storm and inflammation vs. possible immunosuppression and transplant rejection.

A "Clinical Trial to Evaluate Methylprednisolone Pulses and Tacrolimus in Patients With COVID-19 Lung Injury" started in April 1, 2020. Still in its recruiting stage, it is a randomized parallel study using Tacrolimus at doses necessary to obtain blood levels of 8-10 ng/ml alongside 3 days of Methylprednisolone pulses. (Appendix 14)

Recommended dose

The dose for COVID-19 therapy is still to be determined but the ongoing study suggests the dose necessary to obtain trough blood levels of 8-10ng/ml.

Adverse Effects

Commonly seen adverse effects include the following: nephrotoxicity, neurotoxicity (e.g., tremor, headache, motor disturbances, seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes. As with other

immunosuppressive agents, there is an increased risk of secondary tumors and opportunistic infections.[2]

Conclusion

While there is a potential for use, there is limited evidence to evaluate the efficacy and safety of the Calcineurin Inhibitors (Cyclosporine and Tacrolimus) in patients with COVID-19.[9]

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7. 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. As a study on SARS-CoV also 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 Interferon β-1α. There are over 100 countries that are working together in this trial, including the Philippines.[2] Since the last version of this document, there have been more international clinical trials investigating antivirals in the management of COVID-19.

a. LOPINAVIR/RITONAVIR (LPV/r)

Introduction

A protease inhibitor used as an antiretroviral treatment in combination with other antiretroviral agents for HIV 1 in adults and pediatric patients.[3] The updated guidelines of the Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH)for the management of COVID-19 recommends the use of LPV/r in hospitalized patients only in the context of a clinical trial.[4,5] The Surviving Sepsis Campaign (SSC) guideline suggests against the use of LPV/r in critically ill adults.[6] The WHO interim guidance, Australian and New Zealand Intensive Care Society (ANZICS) guideline and National Institute for Health and Care Excellence (NICE) guideline did not address the use of LPV/r in COVID-19.[7]

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[3,8] Ritonavir is used in combination with lopinavir to increase the half-life through the inhibition of cytochrome P450.[8] Protease inhibitors prevent cleavage of the viral polyproteins resulting in the formation of non infectious viral particles.[9]

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.[10]

Clinical Studies

There was no difference in the time to clinical improvement for patients with severe COVID-19 who received LPV/r and standard of care compared to standard of care alone.[11] No significant difference on average lengths of hospital stay nor PCR negative conversion times were observed among adult COVID-19 patients treated with LPV/r-IFN-α and ribavirin-LPV/r -IFN-α combination.[12] A clinical trial for LPV/r as post exposure prophylaxis for those aged 18 months or older is ongoing.[13]

One study in China was intended to recruit 125 adult patients admitted for mild/moderate COVID-19 however, only 86 patients were involved in this study because cases were largely controlled in the country at the time of study. The results showed that LPV/r and arbidol did not shorten the time of positive-to-negative conversion of COVID-19 nucleic acid in respiratory specimens nor did they improve the symptoms of COVID-19 or pneumonia on lung CT imaging at 7 days and 14 days. Moreover, more patients treated with LPV/r progressed from mild/moderate to severe/critical status compared to other groups in study (ELACOI study NCT04252885).[14] Aside from the WHO Solidarity trial, 2 other large clinical trials are going to investigate LPV/r for COVID-19. One is called the RECOVERY trial, sponsored by the University of Oxford in the UK[15] and a multi center trial in Australia, comparing LPV/r to the local standard care called ASCOT Trial.[6]

As of May 10, 2020 there are 38 registered clinical trials investigating LPV/r for its use in COVID-19 management. (Appendix 15-A)

Recommended Dose

Adult dose: 400mg/100 mg twice a day for 10days[16] or 14 days[11].
Pediatric dose: 7-15kg: 12mg/3mg/kg; 15-14kg: 10mg/2.5mg/kg; >40kg: as adult dose as used in clinical trials for COVID-19.
Doses to be taken twice a day for 1–2 weeks.

Adverse Effects and Drug Interactions

Adverse events observed among patients taking LPV/r for COVID-19 were gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal discomfort.[11] It may also cause hepatotoxicity, pancreatitis & ECG abnormalities.

Drug interactions are common with LPV/r due to their inhibition of cytochrome P450 that may result in increased plasma concentrations of other co administered drugs, consequently, leading to the therapeutic and adverse effects as well. Drugs that are contraindicated for use with LPV/r include alpha-1 adrenergic agonists (alfuzosin, prazosin, tamsulosin), neuroactive drugs (midazolam, triazolam, phenobarbital, phenytoin, carbamazepine), drugs for cardiovascular conditions (amiodarone, bepridil, flecainide, propafenone, quinidine, dronedarone, sildenafil), cholesterol lowering agents (lomitapide, lovastatin, simvastatin), antimicrobials (rifampicin, itraconazole,

ketoconazole, metronidazole, elbasvir/grazoprevir), antihistamine terfenadine & astemizole, fluticasone, colchicine, ergot derivatives, ethinyl estradiol/ norethindrone acetate. [17,18]

b. RIBAVIRIN/RBV

Introduction

Ribavirin is a broad-spectrum antiviral drug that hinders viral replication and spread.[19] It is primarily used for Respiratory Syncitial Viral infection, Influenza virus and chronic Hepatitis C.[1,20] A study on patients with SARS treated with LPV/r and ribavirin had a lower risk of ARDS and death compared with monotherapy.[21] Most published international recommendation guidelines for the treatment of COVID-19 have not included ribavirin in their reports on treatment for COVID-19.[7]

Mechanism of Action

In a review of nucleotide inhibitors, RBV was found to cause human Coronavirus eradication in vitro.[22] For SARS patients, it is effective as prophylaxis and as treatment when combined with IFN-b.[23] Ribavirin has also been found to reduce macrophage activation, diminish Th2 cytokine production and preserve Th1 cytokine production among patients with hepatitis C virus.[24]

Clinical Trials

Ribavirin is presently included in the general treatment of COVID-19 in Chinese treatment guidelines[16]

No significant difference on average lengths of hospital stay nor PCR negative conversion times were observed among adult COVID-19 patients treated with LPV/r-IFN-α and ribavirin-LPV/r -IFN-α combination.[12]

There are 3 registered clinical trials, with 2 studies currently recruiting. There is one completed study done in Hong Kong that evaluated the safety and efficacy of ribavirin combined with LPV/r + interferon, with results still to be published. (Appendix 15-B).

Recommended dose

500mg intravenous infusion for adults 2 to 3 times/ day in combination with IFN-α or lopinavir/ritonavir for not more than 10 days.[16]

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.[25]

c. UMIFENOVIR (ARBIDOL)

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.[26] Most published international recommendation guidelines for the treatment of COVID-19 did not address umifenovir in their reports on treatment.[7]

Mechanism of Action

Umifenovir has also been reported to produce an immunomodulatory response by inducing interferon production and stimulating the phagocytic function of macrophages.[21] Umifenovir prevents the fusion of the viral membrane with the endosome after endocytosis.[26]

Clinical Trials

A retrospective cohort study showed clinical & radiologic improvement as well as faster virologic clearance among those who received combination of Arbidol-empirical treatment compared to empirical treatment alone. [27] These findings were seen in those with mild COVID-19 pneumonia but not in severe cases. Empirical treatment used was composed on antivirals such Interferon-α, lopinavir/ritonavir, favipiravir, ribavirin and darunavir/cobicistat.

Results of a case-control study showed that Arbidol, given as post-exposure prophylaxis to family members or healthcare workers, has a potential protective effect against COVID-19 infection. It may have the potential to be used as a post-exposure prophylaxis treatment.[28]

One study analyzed the efficacy and safety of Arbidol monotherapy and lopinavir/ritonavir in 50 patients with COVID-19 and found that no viral load was detected in the Arbidol group after 14 days.[29] At the time of writing, there are a total of 6 registered clinical study for arbidol in COVID-19 patients, with 3 studies currently enrolling participants. However, there are no other published results available at the time of writing. (Appendix 15-C)

Recommended dose

200mg PO, 3 times a day, for not more than 10 days.[15]

Adverse Effects

Some of the reported side effects are diarrhea, dizziness, and elevated serum transaminase, occasional bradycardia.[26]

d. 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.[20] It is currently being investigated in clinical trials and is also available through expanded access and compassionate use for certain patient populations. The IDSA & NIH guidelines did not recommend either for or against the use of remdesivir in COVID-19 as they will await the results of ongoing trials before they make any recommendations.[4,5,30] Other international guidelines did not address remdesivir in their reports.

Mechanism of Action

Remdesivir, a nucleotide analog drug that needs to be converted into its active triphosphate form, inhibits the SARS-CoV-2 RNA dependent RNA polymerase (RdRp) activity, terminating its replication and subsequent decrease in viral RNA production.[31]

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]

Clinical Trials

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. Phase III trials are underway to evaluate the efficacy and safety of remdesivir in patients with mild or moderate and severe COVID-19 respiratory disease.

A preliminary report from a study for the compassionate use of remdesivir in 53 severe COVID-19 patients noted clinical improvement in 68%. During a median follow-up of 18 days, 68% of the patients had improved in oxygen-support, and 57% of patients on mechanical ventilation were extubated.[32]

In a randomized, double-blind multicenter placebo-controlled trial of 237 severe COVID-19 patients, there were no statistically significant benefits observed for remdesivir treatment beyond those of standard of care treatment. However, the trial did not attain the predetermined sample size of 452 subjects because the outbreak of COVID-19 was brought under control. The study also stated that the dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in severe COVID-19. [33]

A preliminary report from The Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the NIAID indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo. The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group.[34]

As of May 10, 2020, there are 12 registered clinical studies on remdesivir, with 8 studies, currently recruiting patients. In China, one study was terminated and another one was suspended because there were no more cases to recruit due to control of COVID-19 in the country. (Appendix 15-D)

Recommended dose

Adult Dose: 200 mg loading dose on day 1 followed by 100 mg IV once-daily for 4 - 9 days as used in clinical trials for COVID-19.

Pediatric doses of remdesivir are used in patients with Ebola.[9] No data for use in pediatric COVID-19 patients.

Adverse Effects

Common adverse events in COVID-19 patients were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. Adverse events were more common in patients receiving invasive ventilation. [32]

e. FAVIPIRAVIR / T-705/ FAVIPIRA/ FAVILAVIR

Introduction

Favipiravir is approved for treatment of novel influenza on February 15, 2020 in China and is currently undergoing clinical trials in treating COVID-19.[9] Most published international recommendation guidelines for the treatment of COVID 19 have not included favipiravir in their reports on treatment for COVID-19.[7]

Mechanism of Action

Resembling guanosine, its action is similar to remdesivir inhibiting the RNA-dependent RNA polymerase of RNA viruses, through competitive inhibition, the efficacy of viral replication can be hugely reduced.[1,35] 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.[35]

Clinical Trials

Favipiravir given to COVID-19 patients resulted in higher clinical recovery rate and earlier relief of cough and fever compared to those given Arbidol. One limitation of this study is the diagnosis of COVID-19 without virologic tests. As such, included patients may have pneumonia due to other pathogens.[36]

The treatment with favipiravir of patients with moderate COVID-19 resulted in significantly shorter viral clearance time and Improvement in CT scan findings compared to LPV/r treatment.[37]

There are 18 registered studies on favipiravir for COVID-19, with 3 studies presently enrolling. (Appendix 15-E)

Recommended dose

1600mg 2x a day on day 1, then 600 mg 2x a day on days 2 to day 14 [37]

Adverse Effects

Some of the adverse effects are raised serum uric acid, abnormal liver function tests, psychiatric symptom, GI disturbance. It is contraindicated for known or suspected pregnant women and lactating women[37,38]

f. OSELTAMIVIR

Introduction

Oseltamivir is a viral neuraminidase inhibitor used for the treatment and prophylaxis of Influenza A, H1N1 Influenza A and Influenza B for both the pediatric and the adult population.[39] It was used widely during the initial phase of the COVID-19 outbreak in China because of concurrent peak influenza season. A large proportion of patients received empirical oseltamivir therapy until the discovery of SARS-CoV2.[40] In Egypt, Oseltamivir is included in their standard of care treatment for confirmed COVID-19 patients.[41]

Mechanism of Action

Oseltamivir is a potent and selective inhibitor of influenza virus neuraminidase enzymes. Inhibiting the neuraminidase enzyme reduces viral shedding and infectivity by hampering the viral entry into uninfected cells, the release of recently formed virus particles from infected cells and further spread of the virus.[39] An initial in vitro study on COVID-19 inferred oseltamivir, combined with other antivirals lopinavir and ritonavir, may be highly effective against COVID-19 and suggested further investigation.[42] However, a more recent in vitro study showed oseltamivir to have no antiviral effect against COVID-19.[43]

Clinical Trials

The WHO interim guidelines on clinical management of suspected COVID-19, has no recommendation on the use of oseltamivir. It has no role in the management of COVID-19 once influenza has been excluded.[30,43] Several of the current clinical trials include oseltamivir in the comparison group but not as a proposed therapeutic intervention.

As of May 10, 2020, there are 11 registered clinical trials involving oseltamivir in COVID-19, with 5 trials presently recruiting subjects. Four of these studies include

oseltamivir in the comparison group as a part of the standard therapy for COVID-19 patients in Egypt. (Appendix 15-F)

Recommended dose

300mg PO per day for 10 – 14 days used in a clinical trial for COVID-19 in Bangkok [44] or 75mg PO every 12 hours for 5-10 days[41] as used in Egypt's treatment guideline for COVID-19.

Adverse Effects

Oseltamivir adverse effects reported are nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children.[45]

CONCLUSION FOR THE SIX ANTIVIRALS DISCUSSED

Antivirals may also have an immunomodulatory role for COVID-19 cytokine storm. More biomolecular studies have to be done to establish this effect. At present there are no recommendations for the use of antiviral medication for the treatment of COVID-19 outside of clinical trials.

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8. ASPIRIN

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), with Aspirin (ASA) as the prototype, are widely used as a first line minor pain medication and also for their antipyretic effects in acute febrile infections. In addition to their anti-inflammatory function they often may have also complex immunological effects on cell proliferation, migration, antibody, and cytokine production.[1]

Mechanism of Action

There are several proposed mechanisms by which ASA can enhance the immune response to viral infections. These include the following: prostaglandin (PG) inhibition via the cyclooxygenase pathway, altered leukocyte migration, activation of complement components, and induction of interferon.[2]

In the light of hyperinflammation, sometimes presenting with cardiac dysfunction and hypercoagulability in COVID-19 cytokine storm, aspirin may have a potential as an immunomodulatory agent. Aspirin has the triple effects of inhibiting virus replication, being an anticoagulant and an anti-inflammatory. Its use is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and decrease the incidence of cardiovascular complications. However, it has not received attention in the treatment and prevention of COVID-19 pneumonia.[3]

Clinical trials

There are no published studies on the efficacy and safety of Aspirin for the management of patients with COVID-19. Clinical trials on Aspirin are currently registered for the treatment of COVID-19. (Appendix 16).

Recommended Dose

No recommended dose yet. However, in the ongoing trials of Aspirin in COVID-19 treatment, 75 to 100 mg of ASA is used.[3,4,5,6,7]

Adverse Effect

The commonly reported side effects include dyspepsia, bleeding and bruising. Some may also experience hypersensitivity reactions that may range from urticaria to anaphylactic shock. Transient elevation of liver enzymes, hepatitis, Reye syndrome, hepatic insufficiency, renal insufficiency and hearing loss and tinnitus (at very high doses) have also been reported.[8]

Conclusion

Given the current lack of existing evidence, no firm scientific conclusion can be made on the efficacy and safety of Aspirin to treat COVID-19 infection. Results of ongoing clinical trials should help to clarify if ASA will have widespread clinical value in prevention and perhaps in the treatment of viral diseases like COVID-19.

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9. AZATHIOPRINE

Introduction

Azathioprine (AZA) is an antagonist of purine metabolism, that inhibits DNA, RNA and protein synthesis. It is an immunosuppressive agent used for the treatment of rheumatic diseases, inflammatory bowel diseases and the prevention of organ transplant rejection.

Mechanism of Action

Azathioprine is a prototypic immunosuppressive antimetabolite. It is a prodrug of mercaptopurine that is well-absorbed from the gastrointestinal (GI) tract. Azathioprine is cleaved by xanthine oxidase to 6-thiouric acid.[1-2]

Once metabolized, azathioprine exerts its immunosuppressive effects by inhibition of purine and protein synthesis in lymphocytes.[3] This reduction in intracellular purine synthesis inhibits the proliferation of T and B lymphocytes, leading to decreased production of cytotoxic T lymphocytes and plasma cells, reduced immunoglobulin synthesis[4] and diminished interleukin (IL)-2 secretion.[5] AZA does not reduce serum levels of IL-6 or soluble IL-2 receptor.[6]

So far, there are no articles indicating the potential of Azathioprine in suppressing COVID-19 cytokine storm.

Clinical Studies

Currently, there are no clinical trials on the use of Azathioprine for COVID-19.

Recommended Dose

No recommended dose as of yet.

Adverse Effects

The most common side effects of AZA at doses typically used in the treatment of rheumatic diseases include gastrointestinal intolerance[2], bone marrow suppression[7], and infection. [8-9]

The major side effects include dose-dependent myelosuppression, particularly leukopenia. Azathioprine should be temporarily withheld if the white cell count falls below 3000/mm^3 or drops by 50 percent compared with the previous value. Other potentially serious side effects include hepatotoxicity and pancreatitis.

Conclusion

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

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10. COLCHICINE

Introduction

Colchicine is an anti-inflammatory drug used for the treatment of acute gout and other inflammatory conditions such as Mediterranean fever, Behcet's disease, myocarditis[1] and pericarditis[2].

Mechanism of Action

Colchicine exerts its anti-inflammatory function by blocking the cytoskeletal function of the cell.[3] The first step in the life cycle of SARS-CoV-2 in the host is attachment.[4] The virus enters the cell by binding of the viral protein S with the cellular receptors of the host cells. What follows is penetration whereby the virus enters the host cells through endocytosis or membrane fusion. By inhibiting β-tubulin polymerization into microtubules, colchicine decreases endocytosis thereby decreasing the viral infection of the host cells.[5] Furthermore, direct anti-inflammatory effects have been shown by inhibiting the NLRP3 inflammasome and other pro-inflammatory cytokines.[6]

Clinical Studies

As of this writing, there are no published results of any clinical trial involving colchicine in the treatment of COVID-19. There are ten registered clinical trials using colchicine, either alone or in combination with standard treatment. (Appendix 17)

Recommended Dose

The recommended dose of colchicine used in the actively recruiting clinical trials is colchicine 1-1.5 mg loading dose followed by 0.5mg tab BID for 7-28 days.[7]

Adverse Reactions

Colchicine is generally well-tolerated. The most frequent adverse reactions involve the gastrointestinal tract such as diarrhea, nausea, vomiting and abdominal pain. Other reported adverse reactions include myelosuppression, disseminated intravascular coagulation, and injury to the cells of the renal, hepatic, circulatory and central nervous systems.

Conclusion

There are no completed clinical trials for colchicine in COVID-19. Results of the ongoing clinical trials will clarify the role of colchicine as a treatment option in the management of COVID-19.

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11. ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Introduction

The Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blockers (ARB) are indicated for hypertension, congestive heart failure and kidney diseases. They reduce the vasoconstrictive, proinflammatory and pro-oxidative effects of angiotensin II (Ang II) levels of the renin angiotensin system (RAS).[1,2]

Mechanism of Action

The RAS pathway begins when renin breaks down angiotensinogen to Angiotensin I (Ang I). The cleaving of Ang I to angiotensin II (Ang II) is facilitated by Angiotensin converting enzyme (ACE). The activation of Type 1 angiotensin II receptor (AT1R) by Ang II, increases sympathetic tone, vasoconstriction, elevation in blood pressure, inflammation, fibrosis, and cardiac hypertrophy.[2,3]

The counter-regulatory mechanisms of the RAS occur by activating the angiotensin converting enzyme 2 (ACE2) – angiotensin 1-7 (Ang1-7) – Mas proto oncogene receptor (MasR pathway). This pathway (ACE2/Ang1-7/MasR) is activated by (ACE2) which hydrolyzes Ang II and generates (Ang1-7). The binding of the Ang I-7 to the MasR causes vasodilation, decrease in blood pressure, helps maintain homeostasis and has an anti-inflammatory effect.[2, 4.]

The ACE2 is a membrane bound aminopeptidase with a homologous structure to ACE but with distinct enzyme active sites.[5,6,7]

Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blockers (ARB) facilitate this counter-regulatory pathway of the RAS.[8] Angiotensin Converting Enzyme Inhibitors (ACEI) prevents the conversion of Ang I to Ang II.[9] Angiotensin II Receptor Blockers (ARB) prevents Ang II from binding to Ang II receptors on the muscles surrounding blood vessels.[9]

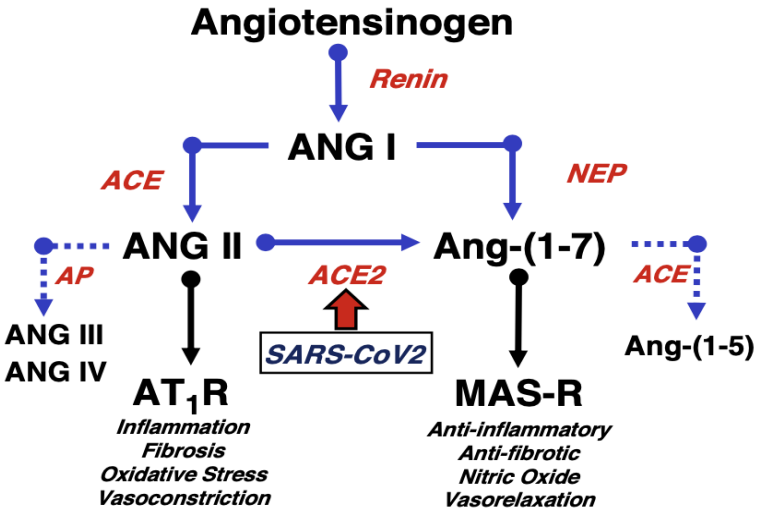

Fig. 1 Processing and Functional scheme of the Renin-Angiotensin system [4]

Effect on COVID-19

The ACE2 is a known co-receptor of SARS-COV2 to gain viral entry into the target epithelial cells of the lungs, intestines, kidneys, heart, and blood vessels.[6,7]

Experimental studies have shown that SARS-CoV cause lung injury through downregulation of the lung ACE2 and in turn, shifts the balance toward the dominance of the RAS over the ACE2/Ang1-7/MasR system in the lung. As a result, noncompeting ANG II accumulation occurs, resulting in acute lung injury through AT1R activation.[10]

RAS modulation with ACEI/ARB or recombinant ACE leads to increased expression of ACE2. Hypothetically, this could increase the viral load and possibly worsen the clinical outcome of COVID-19 patients. Human studies, however showed a lack of association between increased ACE2 protein expression and the use of ARBs or ACEIs.[11] The evidence of ACE2 upregulation is limited only to animal studies using relatively high doses of several ARBs and one ACEI.[4]

Clinical Studies

Studies are ongoing on the benefits vs the risks in the utilization of ACEI/ARB among patients with cardiovascular disorders infected with COVID-19. (Appendix 18)

Recommended Dose[11]

Drug	Initial Dose adult dose	Maximum Dose adult dose
Angiotensin II Receptor Blockers		
Losartan	50 mg	100 mg
Valsartan	80 mg	320mg
Angiotensin Converting Enzyme Inhibitors		
Lisinopril	10 mg	40 mg
Ramipril	2.5 mg	20 mg
Enalapril	5 mg	40 mg
Captopril	50 mg	450 mg

Adverse Effects: [9]

Some of the common adverse effects of ACEI are cough, hyperkalemia, hypotension, kidney failure, pancreatitis, allergic reactions, angioedema.

The ARBs on the other hand may cause hyperkalemia, cough, hypotension, dizziness, headache, drowsiness, metallic taste, kidney failure, liver failure and allergic reactions.

Conclusion

We have to continue to monitor the ongoing studies on the benefits vs. the risks in the utilization of ACEI/ARB among patients with cardiovascular disorders infected with COVID-19. Scientific societies in the US and Europe namely American Heart Association, American College of Cardiology, Heart Failure Society of America, Council on Hypertension of European Society of Cardiology have stated that (in patients with COVID-19) these agents should be maintained in those using them rather than withdrawing these drugs until studies are completed.[12,13]

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12. STATINS

Introduction

A recent meta-analysis showed that risk factors for severe and fatal cases include age over 65 years old, smoking, comorbidities such as hypertension, diabetes, and cardiovascular and respiratory diseases.[1,2,3] Most of these patients with comorbidities are already on statin therapy. Some studies have shown that statin use has been associated with favorable outcomes in patients with influenza and viral pneumonia.[3,4,5] The European Society of Cardiology guidance for the diagnosis and management of cardiovascular diseases during the COVID19 pandemic does not discourage discontinuation of statins except in patients with severe rhabdomyolysis and increased liver enzymes.[5] Moreover, medical professionals in the Massachusetts General Hospital likewise recommend the continuation of statins in COVID 19 patients.[3]

Mechanism of Action

Statins are proven to be beneficial in patients with cardiovascular diseases, because of their anti-inflammatory and anti-oxidative stress actions besides their lipid-lowering activity.[4] They also modulate cell adhesion and migration, antigen presentation, and cytokine production. Moreover, statins can likewise downregulate proinflammatory transcription factors such as NF-Kb through inhibition of MYD88 pathway. In SARS-CoV infection, it has been determined that interaction of the virus with the toll-like receptors activates the NF-Kb which triggers inflammatory pathways.[3,4]

After entering the cells thru ACE2 receptors, SARS-CoV2 downregulates ACE2 expression causing unopposed angiotensin II accumulation which leads to organ injury. Statins are known to upregulate ACE2 via epigenetic modifications. An increase in the ACE2 might be beneficial to COVID-19 patients.[4]

Clinical Studies

Currently there is no clinical evidence of beneficial use of statins in COVID19 patients. However, 2 studies on atorvastatin in COVID-19 patients are underway. (Appendix 19)

The first study is a prospective multicenter randomized controlled trial on preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy. Atorvastatin will be continued or added to the standard of care. Recruitment is ongoing for an estimated 3170 participants.

The second study is a double blind randomized trial that aims to investigate the effect of atorvastatin in the clinical and laboratory findings of patients with COIVD-19. Patients without prior history of cardiovascular disease nor statin use were recruited between April 5-13, 2020. Atorvastatin 40mg 1 tablet once a day for 5 days will be given in addition to standard of care.

Currently, there are no studies on the safety of statins in COVID-19.

Recommended Dose

Adults:	Atorvastatin 40mg once a day
	Rosuvastatin 20mg once a day
	Pravastatin 80mg once a day
Pediatrics:	No data

Adverse Effects

Most statins undergo hepatic metabolism through CYP3A4. Concomitant intake of CYP3A4 inhibitors such as ritonavir and cobicistat in COVID-19 may cause muscle and liver toxicity. Liver injuries appear to be more common in severe COVID-19 cases according to studies. Therefore, starting statins at a lower dose is recommended in these instances, while monitoring the creatine kinase and transaminases.

Statins are generally safe medications with optimal tolerability profile, based on years of extensive clinical research and experience.[3,4]

Conclusion

Theoretically, statins may potentially benefit COVID-19 patients because their immunomodulatory effects were extensively studied in other diseases. They are relatively well-tolerated, affordable and widely available. However, given the lack of current evidence in COVID-19, their use as an immunomodulatory treatment is still inconclusive pending research results.

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13. ALPHA 1 ADRENERGIC RECEPTOR ANTAGONISTS

Introduction

Catecholamines, epinephrine (Epi) and norepinephrine (NE) are critical for initiating the "fight or flight" response of the sympathetic nervous system.

The sympathetic nervous system regulates human immune system functions through (Epi) and (NE) activation of adrenergic receptors (AR) expressed on immunocompetent cell populations.[1,2] which brings to light the possible immunomodulation is catecholamine blockade.

Mechanism of action

The AR family has three types, α_1, α_2, and β- and each further characterized into nine subtypes. All three AR types are expressed in the immune system and are considered immuno reactive (able to mount an immune response to haptens or antigens) when activated by Epi or NE.

AR activation serves many functions in the immune system including modification of depth and breadth of immune response.[1,2,3,4,5] Hence, theory is that administration of selective alpha 1 receptor antagonists may provide an immunodulatory response in human subjects.[4,5,6,7]

Several murine studies have shown that administration of AR antagonists decreased expression of monocyte intracellular adhesion molecules and CD40 expression.[7] Migration of immature Langerhan cells, skin dendritic cells to the lymph nodes[8] were also diminished. The investigators were able to show that pharmacologic blockade of catecholamine with metyrosine protected mice from lethal complication of cytokine release syndrome resulting from infections and biotherapeutic agents.[9] Two studies, one in 2002 and another in 2009, showed that mice pre-treated with prazosin prior to LPS injection had increased levels of anti-inflammatory cytokines (IL-10).[10, 11]

In humans however, adrenergic receptors blockade diminished monocyte migration[12], and modulated complement component C2, particularly prazosin and phentolamine.[13,14]

Taking into consideration these findings, it is noteworthy to establish if they should translate into similar clinical consequences in humans.

Clinical Studies

Konig and colleagues[14] in a preprint article, examined the possible role of cathecholamine blockade in clinical outcomes of patients with COVID-19. A retrospective analysis was made, looking at two cohorts of hospitalized patients. The retrospective analysis included 45-64 year old male patients who filled an ☒1-AR antagonist prescription (doxazosin, prazosin, silodosin, terazosin, or tamsulosin) for more than an aggregate of 180 days in the year preceding the event.

The first cohort consisted of patients with pneumonia. Results showed that those patients with prior use of ☒1-AR antagonists had 12.9% lower incidence of invasive

mechanical ventilation compared to non-users (OR = 0.86, 95% CI 0.78-0.95, p = 0.002; AOR = 0.83, 95% CI 0.75-0.92, p < 0.001). Further, those patients had a 16.0% lower incidence of both being ventilated and dying in the hospital (OR = 0.84, 95% CI 0.68-1.02, p = 0.044; AOR = 0.77, 95% CI 0.62-0.94, p = 0.007).

The second cohort consisted of patients with acute respiratory failure including ARDS. . Their findings showed that patients with prior use of ☒1-AR antagonists had 22.2% lower incidence of invasive mechanical ventilation compared to non-users (OR = 0.75, 95% CI 0.59-0.94, p = 0.008; AOR = 0.75, 95% CI 0.59-0.95, p = 0.009).

Perhaps more importantly, those patients had a 36.0% lower incidence of both being ventilated and dying in the hospital (OR = 0.63, 95% CI 0.37-1.01, p = 0.037; AOR = 0.59, 95% CI 0.34-0.95, p = 0.021). The authors concluded that their findings mirrored those of pre-clinical models. These may support the use of alpha 1 receptor antagonists in the preventing severe complications of pneumonia, ARDS in COVID-19.

Currently, Johns Hopkins University will be spearheading an open label randomized study on the role of prazosin in 220 Covid19 positive patients. Prazosin shall be given at incremental doses and outcome measures to be determined will include hospitalization requiring mechanical ventilation or supplemental oxygen and incidence of grade 3 and 4 adverse events.[15] (Appendix 20)

Recommended Dose

Prazosin at an initial dose of 1 mg every 8 hours will be administered to patients included in the study. The dose shall be adjusted accordingly according to possible blood pressure changes every three days. The maximum dose to be used will be 5 mg q8.[15]

As of May 10, 2020, there are no specific studies addressing the use of alpha-1 adrenergic receptor antagonists for treatment in the pediatric population.

Adverse Effects

The most common side effect is postural hypotension. All of the alpha-1 adrenergic receptor antagonists are associated with a minimal rate of serum hepatic enzyme elevations during chronic therapy (0.2% to 2%). These elevations are almost always mild-to-moderate in severity, self-limited, and do not require dose modification or drug discontinuation.[16]

Conclusion

The complete and extensive role of this receptor in modulating immune responses is still in its infancy. Hence, future studies are still required to further elucidate the depth and breadth of its involvement and therapeutic potential in human subjects with COVID-19.

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14. 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 21)

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.

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15. 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]

There are currently, two randomized placebo controlled trial phase 3 that are actively recruiting subjects as of May 10, 2020. (Appendix 22)

The primary intention of the studies are to document the possible non - specific protective effect of BCG vaccine and reduction of the impact of COVID-19 virus among healthy health care workers exposed during the COVID-19 pandemic.

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.

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16. INOSINE PRANOBEX

Introduction

Inosine pranobex is a synthetic compound of the p-acetamido-benzoate salt of N-N dimethylamino-2-propanol with inosine in a 3:1 molar ratio. It is also known as inosine acedoben dimeprano, Isoprinosine or methisoprinol. [1]

Researches have shown that it has antiviral and immunomodulatory properties.[1]

Mechanism of Action

Immunomodulatory property

Inosine pranobex induces TH1 response resulting to T lymphocyte maturation, differentiation and enhanced lymphoproliferative response. It also regulates activity of CD8+ suppressor and CD4+ helper cells functions . It increases levels of IL-2, interferon-gamma and tumor necrosis factor -alpha while levels of IL-4,IL-5 and IL-10 were decreased. It also improved neutrophil chemotaxis and phagocytosis [2,3,4,5,6]. Its effect in regulating T helper cells leads to stimulation of B cells to differentiate into plasma cells leading to an enhanced antibody production [7,8].

Antiviral property

Inosine pranobex also showed an increase in the level of natural killer (NK) cells with increased activity.[5,6] It was also observed to inhibit replication of several RNA and DNA viruses.[9]

Clinical Studies

No clinical studies have been conducted yet for the treatment of COVID-19. There is one clinical trial, though, on its use as immunoprophylaxis for healthcare workers with exposure to COVID-19. This, however, is beyond the scope of this review.

Recommended dose

The usual dose ranges from 25 to 100 mg/kg in single or divided doses. [11,12,13]

Adverse Effects

Inosine pranobex has a good safety profile with reported adverse events lower than the placebo group.[10]

Conclusion

There are no studies conducted on the use of inosine pranobex for treatment of COVID-19 cytokine storm.

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17. RELEASE ACTIVE ANTIBODIES TO HUMAN INTERFERON GAMMA (ANAFERON)

Introduction

Release active antibodies to human interferon gamma (IFN-γ) known as Anaferon is a drug that acts as an immunomodulator and antiviral agent. It exerts its antiviral effect through induction of IFN-α/β and its immunomodulatory effect via induction of IFN-γ. [1]

Mechanism of Action

Affinity-purified rabbit polyclonal antibodies to recombinant human interferon gamma were manufactured in accordance with current European Union requirements for Good Manufacturing practice in a mixture of homeopathic dilutions[5]. The mechanism of action of this novel concept is its ability to regulate the functional activity of endogenous interferons. Anaferon acts on IFN-γ and its receptor resulting in macrophage and NK-cell activation leading to lysis and apoptosis of infected cells. It also stimulates T effector cells, Th1 responses and increases concentrations of IgG and secretory IgA. Anaferon also acts by increasing expression of IFN-α/β and related interleukins (IL-2, IL-4, IL-10), to ensure effective antiviral protection without risk of resistance.[2,3,5]

Its potential use for COVID -19 is during the acute phase. The virus triggers active endogenous interferon production. Anaferon triggers molecular and conformational changes and enhances production of IFN-γ and α via positive feedback. Thus, during "peak" viral infections a far larger amount of activated IFN-γ and α molecules are activated and bound to its receptors[7].

Clinical Studies

The spectrum of clinical studies is for therapy and prevention of viral infections. These include influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza, herpes 1 and 2. Some viruses that caused diarrhea like enterovirus, rotavirus, calicivirus and coronavirus were also studied.[1,2,3,4,6]

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

Adverse Effects

There were no adverse effects related to the drug in clinical trials. Special precautions to patients with galactose intolerance, lactase deficiency and glucose-galactose malabsorption due to the presence of lactose in the drug. [1,2]

Recommended Dose

The dose has not yet established for COVID-19. However, as treatment for viral upper respiratory infections the orodispersal tablet is given as follows: within the first day, the drug should be taken every 30 minutes for the first 2 hours, then 3 additional times with regular intervals (total of 8 tabs). From day 2-5, the drug is taken three times a day.[7]

Conclusion

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

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18. 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 23)

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.

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b. VITAMIN D

Introduction

Vitamin D is a fat-soluble vitamin that needs to undergo 2 hydroxylation processes to become active. The first occurs in the liver where Vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], or calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol.[1]

Mechanism of Action

Vitamin D enhances the cellular innate immunity through induction of cathelicidin by 1,25 dihydoxyvitamin D and defensins. The cathelicidins kill the invading pathogens by perturbing their cell membrane and neutralize the biological activity of endotoxin. [2,3]

It reduces TNFα and Interferon gamma,[4] as well as other inflammatory cytokines such as IL-2.[5]

Calcitiriol, (1,25$(OH)_2D_3$) promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types.[6] Furthermore, calcitiriol promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes.[7]

Clinical Studies

There are 3 ongoing studies, 2 randomized trial and 1 observational study. Studies are still in the recruitment phase. (Appendix 24)

Recommended Dose: [1,8]

Infants:	8.5 to 10 ug/day or 400IU
1year to 70 years:	10ug/day or 600IU
>70 years:	20ug/day or 800IU

Adverse Effects

Vitamin D toxicity can cause anorexia, weight loss, polyuria, and heart arrhythmias. It can also raise blood levels of calcium which leads to vascular and tissue calcification, with subsequent damage to the heart, blood vessels, and kidneys.[9]

Conclusion

Studies on the use of Vit D on COVID-19 are ongoing and awaiting results of its benefits among COVID-19 patients.

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c. 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] (Appendix 25)

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.

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d. 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.

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e. 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.

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f.

f. PROBIOTICS

Introduction

Probiotics are defined by the World Health Organization as living microbial agents of human origin that are able to tolerate the hostile gastrointestinal environment (acid and bile) such that they ultimately persist in the lower alimentary tract to confer health benefits to the host [1]

Probiotics are living microorganisms that confer health benefits to the host when administered in adequate amounts; however, dead bacteria and their components can also exhibit probiotic properties. Bifidobacterium and strains of lactic acid bacteria are the most widely used bacteria that exhibit probiotic properties and are included in many functional foods and dietary supplements.[2]

Probiotics have been shown to prevent and ameliorate the course of digestive disorders such as acute, nosocomial, and antibiotic-associated diarrhea; allergic disorders such as atopic dermatitis (eczema) and allergic rhinitis in infants; and Clostridium difficile-associated diarrhea and some inflammatory bowel disorders in adults. In addition, probiotics may be of interest as co-adjuvants in the treatment of metabolic disorders, including obesity, metabolic syndrome, nonalcoholic fatty liver disease, and type 2 diabetes.

In China, 58–71% of patients with COVID-19 were given antibiotics, and diarrhoea occurred in 2–36% of patients. When antibiotics are used, reinforcement of colonic flora using probiotics has been proposed to reduce susceptibility to subsequent infections.[3]

Mechanism of Action

The mechanisms of action of probiotics are diverse, heterogeneous, and strain specific, and have received little attention. One of the major mechanisms of action of probiotics is the regulation of host immune response. The immune system is divided into the innate and adaptive systems. The adaptive immune response depends on B and T lymphocytes, which bind to specific antigens. In contrast, the innate system responds to common structures, called pathogen-associated molecular patterns (PAMPs), shared by a majority of microbes.

The primary response to microbes, such as probiotics, is facilitated by pattern recognition receptors (PRRs), which bind to PAMPs. Toll-like receptors (TLRs), which are types of PRRs, are transmembrane proteins that are expressed on various immune and nonimmune cells, such as B-cells, natural killer cells, DCs, macrophages, fibroblast cells, epithelial cells, and endothelial cells. Activation of TLRs are known to facilitate activation of the innate immune response, and, consequently the adaptive immune response.

Probiotics help to preserve intestinal homeostasis by modulating the immune response and inducing the development of T-regs. Further research to elucidate the precise molecular mechanisms of action of probiotics is warranted.[2]

Clinical Studies

As of April 24, 2020, two randomized controlled trials showed that critically ill patients on mechanical ventilation who were given probiotics (*Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*) developed substantially less ventilator-associated pneumonia compared with placebo.[3,4]

Recommended Dose

2 x 10^9 colony-forming units (cfu) of Lactobacillus rhamnosus GG on a twice-daily basis[1]

Adverse Effects

The potential harms of probiotic therapy also requires investigation. Historically, the consensus has been that probiotic therapy was of questionable value but was safe.[1]

Conclusion

Not all probiotics are likely to be the same. *Lactobacilli* and *Bifidobacteria* are only two types of non-pathogenic bacteria and we must consider whether they can really tip the balance of a diverse gut ecosystem in combating COVID-19. When antibiotics are used, reinforcement of colonic flora using probiotics has been proposed to reduce susceptibility to subsequent infections.

To date, the rationale for using probiotics in COVID-19 is derived from indirect evidence. Blind use of conventional probiotics for COVID-19 is not recommended until we have further understanding of the pathogenesis of SARS-CoV-2 and its effect on gut microbiota. It is likely that a novel and more targeted approach to modulation of gut microbiota as one of the therapeutic approaches of COVID-19 and its comorbidities will be necessary.

However, the efficacy of probiotics in reduction of intensive care unit mortality and inpatient mortality is uncertain.[5]

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g. OMEGA 3 FATTY ACIDS AND DHA

Introduction

Omega-3 Fatty acids, including, Docosahexaenoic acid (DHA), a long-chain omega-3 fatty acid, are predominantly sourced from fishes like salmon, tuna, and mackerel[1]. Increasing consumption is said to offer benefits to those with cardiovascular problems.

Studies have reported anti-inflammatory and immunomodulatory effects of DHA[2]

Mechanism of Action

DHA's anti-inflammatory action is by directly inhibiting pro-inflammatory transcription factors like Nuclear factor kappa beta that increases levels of IL-1beta,IL-6, TNF-alpha and chemokine MCP-1. DHA also inhibits inflammatory mediators such as : VCAM-1, ICAM-1,TNF-alpha,IL-6 and TLR-4.[3,4,5,6]

DHA increases the phagocytic property of macrophages [7] and neutrophils [8], decreased activation of basophils [9], mast cells[10] and T cells[11] and caused an increase in IgM production[12].

Recommended Dose

The American Heart Association recommends 4 g EPA+DHA to lower cholesterol[1], but there are no studies on the immunomodulatory dose.

Adverse Effects

Thromboxane A3 produced by DHA is a less potent platelet activator which may result to an altered platelet function[13]. There is also the possibility of intake of toxins or sea contaminants together with the DHA.[14]

Conclusion

There are no studies on the use of DHA for COVID-19. Human trials are needed to test for its efficacy and safety against COVID-19.

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CONCLUDING REMARKS

As the numbers of the COVID-19 confirmed cases and mortalities rise worldwide, we are tasked to gather the data, review the literature and disseminate evidence-based information. We are thankful that the world continues to share their information on battling COVID-19. We are grateful to the Immunologists who are members of the Philippine Society of Allergy, Asthma and Immunology, Inc. who regularly update and add to this review.

There still is no single immunomodulator nor a combination that stands out as the most effective therapy in dealing with the COVID-19 pandemic. These immunomodulators have been reviewed to assist our dedicated frontliners in the management of COVID-19 patients before or during the Cytokine storm.

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.

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 second version dated May 10, 2020.

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APPENDICES

Tables of Studies using the aforementioned Immunomodulators for COVID-19

Appendix 1. 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	N/A	Patients with COVID 19, severe type 34 – 56y/o (3)	Improvement in clinical status & laboratory parameters	The 3 cases were successfully treated by high-dose IVIG at the early stage of clinical deterioration.	Published	https://academic.oup.com/ofid/article/7/3/ofaa102/5810740
Hu H, et al.	Case report (China)	IVIG Methylprednisolone Norepinephrine Toracemide and furosemide Milrinone Sulbactam Pantoprazol	N/A	37y/o patient with pulmonary infection, enlarged heart, pleural effusion & positive coronavirus nucleic acid test	Improvement in clinical status & laboratory parameters	The authors suggested that early glucocorticoid anti-inflammatory therapy & IVIG therapy may be of important value to this type of patient.	Published	https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa190/5807656
Zhao K, et al.	Case report (China)	IVIG Ganciclovir, Lopinavir/ritonavir, Moxifloxacin, Meropenem, Glutathione, Dexametha-sone, Mecobala-mine, Pantoprazole	N/A	66y/o with COVID-19 who developed acute myelitis	Clinical improvement, discharged for isolation & rehabilitation		Published	https://www.medrxiv.org/content/10.1101/2020.03.16.20035105v2

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
LeVine S, et al.	Case report (Bhutan)	IVIG	N/A	76y/o immunocompromised with history of travel, developed GI symptoms and cough, RT-PCR positive; respiratory status deteriorated despite broad-spectrum antivirals, antibiotics, and intensive supportive care	Improvement in clinical status & laboratory parameters after the first dose		Published	http://www.ajtmh.org/docserver/fulltext/10.4269/ajtmh.20-0259/tpmd200259.pdf?expires=1587712939&id=id&accname=guest&checksum=6CA880001367D37DC5854920EEA24DAF
Shi H, et al.	Case report (China)	Plasma exchange (PE) followed by IVIG	N/A	50y/o with laboratory-confirmed COVID-19 with respiratory failure, shock, persistent diarrhea despite conventional therapy	Improvement in clinical status & laboratory parameters after the 4th dose	Timely initiation of PE treatment followed by IVIG protected the patient from progressing to acute respiratory distress syndrome (ARDS) & multiple organ failure	Published	https://doi.org/10.1016/j.ijantimicag.2020.105974

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Xie Y, et al.	Retrospective study (China)	IVIG < 48 hours after admission	IVIG > 48 hours after admission	COVID 19 with severe or critical illness (58)	28-day mortality	There was a statistically significant reduction in 28-day mortality between the two groups	Published	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151471/pdf/main.pdf
Shao Z, et al.	Retrospective cohort study (China)	IVIG Subgroups: • IVIG >15g/day • IVIG <15g/day • IVIG given >7 days • IVIG given ≤7 days	Standard care	Patients with COVID-19 ≥18y/o Subgroup: -Severe type -Critical type (325)	28-day and 60-day mortality	No improvement in 28-day and 60-day mortality • IVIG significantly decreased the 28-day mortality in critical type patients • high dose IVIG (>15 g/d) significantly reduced 28-day & 60-day mortality • early use of IVIG (≤ 7d) significantly reduced the 60-day mortality	Pre-print	https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v1.full.pdf

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Zhou Z, et al.	Prospective cohort study (China)	IVIG Moderate-dose cortico-steroid	N/A	COVID-19 patients who failed low dose Cortico-steroid (CS) (10)	Improvement in clinical status & laboratory parameters	All patients achieved significant improvement in terms of vital signs, blood work, & the APACHE Ⅱ scores.	Pre-print	https://www.preprints.org/manuscript/202003.0065/v1
NCT04261426	Randomized, open-label, parallel assignment (China)	IVIG	Standard care	COVID-19 patients with severe pneumonia >18 y/o (80)	Clinical improvement based on the 7-point scale, lower Murray lung injury score in 7 & 14 days after randomiza-tion	APACHE Ⅱ scores	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04261426?term=intravenous+immunoglobulin&cond=COVID-19&draw=2&rank=1
NCT04350580	Randomized, double-blind, parallel assignment (France)	IVIG	Placebo (sodium chloride 0.9%)	COVID-19 patients with ARDS meeting the Berlin criteria (138)	Ventilator-free days	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350580?term=intravenous+immunoglobulin&cond=COVID-19&draw=2&rank=4

Appendix 2. 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)	CP	NA	Patients with severe COVID 19 (10)	Safety of CP transfusion; improvement of clinical symptoms & laboratory parameters within 3 days after CP transfusion	No serious adverse events; 10 patients improved in 1-3 days; reduced pulmonary lesion on CT; amelioration of routine blood tests & pulmonary function; Increase IgG & (-) SARS-CoV-2	Completed	https://www.pnas.org/content/early/2020/04/02/2004168117
Shen C, et al.	Case series (China)	CP + anti-viral agents + Methylprednisolone ± IFN α 1b	NA	Critically ill patients with COVID 19 (5)	Before and after CP transfusion: -Changes in body temp. -Sequential Organ Failure Assessment (SOFA) score -PaO2/FiO2 -Viral load, serum ab titers, routine blood tests index -ventilatory/ ECMO support	After CP: -normal body temp. D3 -SOFA score decreased -PaO2/FiO2 improved D7 -CRP, procalcitonin & IL 6 decreased -ARDS resolved D12 -weaned ventilator D14 -discharged/ stable D37	Completed	https://www.ncbi.nlm.nih.gov/pubmed/32219428

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04340050	Open Label, single group assignment (USA)	CP	NA	Patients with COVID 19 ≥18y/o (10)	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 single, parallel assignment (Netherland)	CP	Standard care	Patients with COVID 19 ≥18y/o (426)	Overall mortality until discharge or maximum of 60 days after admission	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04342182
NCT04332835	Randomized, open Label, parallel assignment (Colombia)	CP + Azithromycin + HCQ	Azithromycin + HCQ	Patients with COVID 19 18-60 y/o (80)	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	(Placebo) γ globulin	Patients with COVID 19 ≥18y/o (10)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04264858

Appendix 3. Corticosteroids (CS) Studies for COVID 19

Author/ Study Identifier	Study design (Country)	Intervention	Comparator	Population (Sample size)	Primary outcome	Results	Status	Source (hyperlink)
Wang Y, et al.	Observation-al, retrospective (China)	Methyl-prednisolone	Standard care	Severe COVID 19 pneumonia (46)	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
Zhou ZG, et al	Case series (China)	Methylpredni solone moderate dose + IVIG	NA	Patients with COVID 19 who have failed low dose CS (10)	Reversion of continued deterioration of COVID-19 patients.	Short-term mod-dose CS + IVIG is effective for reversing the continued deterioration of COVID-19 patients.	Completed	https://www.preprints.org/manuscript/202003.0065/v1
NCT04244591	Randomized, open Label parallel assignment (China)	Methypred-nisolone	Placebo Standard care	COVID-19 Critically Ill patient with severe acute respiratory failure ≥18y/o (80)	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
NCT04273321	Randomized, open label, single group assignment (China)	Methyl-prednisolone	Standard care	COVID 19 pneumonia >18y/o (400)	Incidence of treatment failure in 14 days	NA	Recruitment suspended as of Apr 17, 2020	https://clinicaltrials.gov/ct2/show/record/NCT04273321
NCT04323592	Non-randomized, open label, single group assignment (Italy)	Methyl-prednisolone	Standard care	Severe COVID 19 with acute respiratory syndrome 18 - 80y/o (104)	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

Author/ Study Identifier	Study design (Country)	Intervention	Comparator	Population (Sample size)	Primary outcome	Results	Status	Source (hyperlink)
NCT04327401	Randomized, open label, parallel assignment (Israel)	Dexametha-sone	Standard care	COVID 19 associated ARDS ≥18y/o (290)	Ventilator free days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04327401?term=corticosteroids&cond=covid+19&draw=2&rank=3
NCT04325061	Randomized, open label, parallel assignment (Spain)	Dexametha-sone	Standard care	COVID 19 ARDS ≥18y/o (200)	60-day mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04325061?term=corticosteroids&cond=covid+19&draw=2&rank=4
NCT02735707	Randomized, open label, Factorial assignment (REMAP-CAP)	Fixed duration & shock dependent Hydro-cortisone	No systemic Hydro-cortisone	Community Acquired Pneumonia, Influenza, COVID 19 ≥18y/o (7,100)	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 (Spain)	Siltuximab	Methyl-prednisolone	COVID 19 Pneumonia ≥18y/o (200)	Proportion of patients requiring ICU admission at anytime during the study period	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329650?term=corticosteroids&cond=covid+19&draw=2&rank=1
NCT04348305	Randomized quadruple, parallel assignment (Denmark)	Hydrocorti-sone	Placebo (Isotonic saline)	COVID-19 with severe hypoxia ≥18y/o (1,000)	Days alive without life support at D28	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04348305?term=steroid&cond=covid+19&draw=2&rank=1

								&view=record
Author/ Study Identifier	Study design (Country)	Intervention	Comparator	Population (Sample size)	Primary outcome	Results	Status	Source (hyperlink)
NCT04360876	Randomized, double blind, parallel, double blind (USA)	Dexametha-sone	Placebo	COVID-19 with ARDS ≥18y/o (90)	Ventilator free days at D28	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04360876?term=steroids&cond=covid+19&draw=4&rank=3
NCT04355637	Randomized, open Label, parallel assignment (Spain)	Inhaled Budesonide	Standard Care	COVID-19 Pneumonia 18 – 79y/o (300)	Treatment failure	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04355637?term=steroids&cond=covid+19&draw=4&rank=5
NCT04355247	Non-randomized, open label, single group assignment (Puerto Rico)	Methylpredni solone	NA	COVID-19 ≥18y/o (20)	Clinical complete response criteria	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04355247?term=steroids&cond=covid+19&draw=4&rank=6
NCT04331470	Randomized, double blind, parallel assignment (Iran)	Levamizole + Budesonide/ Formoterol Inhaler	Standard care	COVID-19 15 – 100y/o (30)	Clear Chest CT Scan	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04331470?term=steroids&cond=covid+19&draw=4&rank=7

Appendix 4. Anti-malarial agents Studies for COVID 19: Hydroxychloroquine (HCQ), Chloroquine (CQ)

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Chen J, et al.	Randomized, open label, parallel assignment (China)	HCQ	Standard care	Patients with COVID 19 (30)	Negative conversion rate of COVID 19 nucleic acid in respiratory pharyngeal swab on D7 after randomiza-tion.	No significant difference in the following: (-) nucleic acid throat swab; median duration from hospitalize-tion to virus nucleic acid negative conversion; median time for normal body temp; radiological progression in CT images	Published	http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03
Mahévas M, et al.	Observation-al, retrospective (France)	HCQ in 1st 48 hours after hospitalisa-tion	Standard care	COVID-19 pneumonia 18-80 y/o (181)	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 in 7 days: HCQ (2.8%) Non-HCQ (4.6%); Harm w/ QTc prolongation (8), AV block (1), LBBB (1)	Pre print not peer reviewed	https://doi.org/10.1101/2020.04.10.20060699

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Zhaowei C, et al.	Randomized, Open label, parallel assignment (China)	HCQ	Standard care	COVID-19 with pneumonia >18 y/o (62)	Normalization of body temperature, cough relief, CT changes	Normal 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
NCT04261517	Randomized, open label, parallel A assignment (China)	HCQ	Standard care	COVID 19 with pneumonia ≥ 18 y/o (30)	Viral clearance on NPS, sputum or lower resp tract at Day 3,5 & 7; mortality rate of subjects	NA	Completed	https://clinicaltrials.gov/ct2/show/NCT04261517
Gao J, et al.	Randomized control, parallel assignment (China)	CQ	Standard care	COVID 19 (>100)	Clinical improvement	Reduced symptom duration; inhibited pneumonia exacerbation; improved lung function; virus (-) conversion; w/o severe side effects	Completed	https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_article

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Borba MG, et al.	Randomized double blind, quadruple; parallel assignment (Brazil)	CQ (high dosage)	CQ (low dosage) + placebo	COVID 19 ≥18y/o (440)	Mortality rate reduction of 50% by D28	Higher dose CQ + Azithromycin & Oseltamivir is not recommend-ed for critically ill COVID 19; Viral RNA detected: -high (77.5%) -low (75.6%); Lethality until Day 13 (39% in high vs 15% in low dose); QTc prolongation (18.9% high vs 11.1% low dose)	Published	https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499?utm_campaign=articlePDF%26utm_medium%3darticlePDFlink%26utm_source%3darticlePDF%26utm_content%3djamanetworkopen.2020.8857
ChiCTR2000029868	Randomized, open label, parallel assignment (China)	HCQ	Standard care	COVID 19 ≥18y/o (360)	Viral nucleic acid test results;	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49524
ChiCTR2000029741	Randomized open label, parallel assignment (China)	HCQ	LPV/r	Mild COVID 19 ≥18y/o (112)	Length of stay & severe disease; O2 index; all-cause mortality; blood test results, viral nucleic acid test results	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49263

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000029740	Randomized, open label, parallel assignment (China)	HCQ	Standard care	COVID 19 16 – 99y/o (78)	Temperature; max RR; O2 index; lymphocyte count; CXR	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49317
ChiCTR2000029559	Randomized, double blind, parallel assignment (China)	HCQ 2 groups: -0.1g bid -0.2g bid	Placebo (Starch)	COVID 19 30 -65y/o (300)	Viral nucleic acid turns (-); T cell recovery time	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=48880
NCT04307693	Randomized, Open label, parallel assignment (Korea)	HCQ; LPV/r	Standard care	Mild COVID 19 16 - 99y/o (150)	Viral load change	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693
NCT04318444	Randomized' quadruple, parallel assignment (USA)	HCQ	Placebo	Household or in-hospital contact with COVID 19 ≥18y/o (1,600)	COVID 19 symptoms; lab-confirmed COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04318444
NCT04315896	Randomized double blind, quadruple, parallel assignment (Mexico)	HCQ	Placebo	Severe COVID 19 18 – 80y/o (500)	All-cause mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04315896
NCT04323631	Randomized open label, sequential (Israel)	HCQ	Standard care	COVID 19 ≥18y/o (1,116)	# of patients with severe infection or death	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04323631
NCT04318015	Randomized Triple blinded, quadruple, parallel assignment	HCQ	Placebo	Health care workers at risk ≥18y/o (400)	Symptomatic COVID 19 infection rate	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04318015

	(Mexico)							
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04308668	Randomized, quadruple, parallel assignment (USA)	HCQ	Placebo	Participants exposed to COVID 19 within 4 days (3,000)	Incidence of COVID 19; 0rdinal Scale of COVID19 Severity at D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04308668
NCT04321616	Randomized open label, parallel assignment (Norway)	HCQ; HCQ + Remdesivir	Standard care	Hospitalized COVID 19 ≥18y/o (700)	All-cause mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04321616
NCT04321993	Non-randomized open label, parallel assignment (Canada)	HCQ; LPV/r; Baricitinib	Standard care	Moderate – severe COVID 19 ≥18y/o (1,000)	Clinical status of subject at D15	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04321993
NCT04304053	Randomized, Open label, Parallel assignment (Germany)	HCQ as prophylaxis; HCQ as treatment	Standard public health measures; standard case	Contacts with COVID 19; COVID 19 ≥18y/o (3,040)	Incidence of secondary COVID-19 cases; viral clearance & mortality rate	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04304053
NCT04334148	Randomized, double blind, triple, parallel assignment (USA)	HCQ	NA	Health care workers at risk ≥18 y/o (15,000)	# of participants with clinical infection with COVID 19	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04334148
NCT04353271	Randomized, quadruple, parallel assignment (USA)	HCQ	NA	COVID 19 19-85 y/o (58)	% of virus free Subjects; disease Severity	NA	Active Not Recruiting	https://clinicaltrials.gov/ct2/show/NCT04353271
NCT04342156	Randomized, open label, parallel as-signment	HCQ	NA	Adults at risk 18- 80 y/o (1200)	(+) serology or RT-PCR on SARS-CoV-2	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04342156

	(Singapore)							
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04341441	Randomized, triple blinded, parallel assignment (USA)	HCQ	NA	Adults at risk 18-75 y/o (3,000)	Decrease rate of acquisition of COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341441
NCT04342221	Randomized, quadruple, parallel assignment (Germany)	HCQ	NA	Adult with COVID 19 18-99 y/o (220)	Viral clearance by NPS RT PCR (specific RNA $\leq$ 100)	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04342221
NCT04328961	Randomized, double blind, parallel assignment (USA)	HCQ	Vit C	Closed contacts with suspected or confirmed COVID 19 18-80 y/o (2,000)	PCR Confirmed SARS CoV-2 infection	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04328961
NCT04338906	Randomized, quadruple, parallel assignment (Germany)	HCQ	Camostat Mesylate	Hospitalized moderate COVID 19 $\geq$ 18 y/o (334)	Not hospitalized (Day 14 from baseline)	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04338906
NCT04351620	Open label, single group assignment (USA)	HCQ	NA	Outpatient mild COVID 19 $\geq$ 18 y/o (20)	Tolerability of HCQ high dose; adverse events	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04351620
NCT04333225	Non-randomized, open label, parallel assignment (USA)	HCQ	NA	Health care workers at risk 18 – 75 y/o (228)	Rate of COVID (+) conversion on NPS	NA	Active, Not recruiting	https://clinicaltrials.gov/ct2/show/NCT04333225
NCT04361318	Randomized double blind, parallel assignment	HCQ + Nitazoxanide	Standard Care	Newly diagnosed COVID 19 18-65 y/o	# of patients with COVID 19 (-) RT-PCR	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04361318

	(Egypt)			(100)				
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04359537	Randomized, single blind, parallel assignment (Pakistan)	HCQ	NA	Health care workers at risk ≥18y/o (200)	COVID 19 free survival	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359537
NCT04363866	Randomized, single blind, parallel A assignment (USA)	HCQ	NA	COVID 19 ≥18y/o (40)	Clinic Status at D5 by 6-point Ordinal Scale	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04363866
NCT04364815	Randomized, double blind, parallel assignment (Philippines)	HCQ	Standard preventive measures	Health care workers at risk 18 – 59 y/o (960)	Incidence of COVID 19 confirmed by RT PCR	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04364815
NCT04340544	Randomized, quadruple, parallel assignment (Germany)	HCQ	NA	Mild COVID 19 ≥18 y/o (2,700)	Difference in time to resolution of symptoms	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04340544
NCT04369742	Randomized, double blind, parallel assignment (USA)	HCQ	Calcium citrate	COVID 19 ≥18 y/o (626)	Incidence of AE or stopping of therapy; severe disease progression	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04369742
NCT04377646	Randomized, double blind, parallel A assignment (Tunisia)	HCQ	Zinc	Military health professionals at risk 18 – 65 y/o (660)	SARS CoV-2 infection	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04377646
NCT04355026	Randomized, open label, parallel assignment	HCQ	HCQ + Bromhexine	COVID 19 ≥19 y/o (90)	Duration of hospital stay; duration of	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04

	(Slovenia)				disease			355026
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04315896	Randomized, double blind, parallel assignment (Mexico)	HCQ	NA	COVID 19 with severe respiratory distress 18 -80y/o (500)	All-cause hospital mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04315896
NCT04329923	Randomized, open label, parallel assignment (USA)	HCQ	Placebo	COVID 19 ≥18y/o (400)	Median release from quarantine time; rate of hospital discharge & infection of HCW	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329923
NCT04359537	Randomized, single blind, parallel assignment (Pakistan)	HCQ	Placebo	Health care workers at risk 18 – 60y/o (200)	% of COVID 19 free	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359537
NCT04350450	Non-randomized, open label, parallel assignment (USA)	HCQ	Standard care	COVID 19 18-99 y/o (100)	Time to resolution of symptoms	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04350450
NCT04330144	Randomized, single, parallel assignment (South Korea)	HCQ	NA	Health care workers at risk 18 – 99y/o (2,486)	rate of COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04330144
NCT04372082	Randomized, single blind, parallel assignment (Lille, North	HCQ	Diltiazem + Niclosamide	Non-severe COVID 19 with co-morbidities ≥18 y/o	Death; clinical worsening; need for O2 assisted-	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04372082

	Europe)			(480)	ventilation			
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04331834	Randomized, quadruple, parallel assignment (Spain)	HCQ	NA	Health care workers at risk ≥ 18 y/o (440)	Confirmed Case of COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04331834
NCT04307693	Randomized, open label, parallel assignment (South Korea)	HCQ; LPV/r	Standard care	Mild COVID 19 16 - 99 y/o (150)	Viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693
NCT04345692	Randomized, open label, parallel assignment (Hawaii)	HCQ	Standard care	Hospitalized COVID 19 18-95 y/o (350)	Clinical Status on a 7 - point ordinal scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04345692
NCT04346329	Randomized, double blind, parallel assignment (Colombia)	HCQ	Placebo	Health care workers at risk ≥18 y/o (86)	Adverse effects	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04346329
NCT04372017	Randomized, double blind, parallel assignment (USA)	HCQ	Vitamin D	High risk close contact with COVID 19 ≥18 y/o (1,739)	% of COVID 19 (+) healthcare workers	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04372017
NCT04345653	Open label, single Group Assignment (USA)	HCQ	NA	Healthy volunteers at risk 18 - 99y/o (45)	AE; # of participants contracting COVID 19	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04345653
NCT04376814	Non-randomized, open label, parallel assignment	HCQ	HCQ + Favipiravir + Kaletra	COVID 19 with ground glass chest CT scan 16 -100y/o	Admission to ICU	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04376814

	(Iran)			(40)				
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04318444	Randomized, quadruple, parallel assignment (USA)	HCQ	Placebo	Household contact with confirmed or suspected COVID 19 ≥18 y/o (1,600)	# of participants with symptoms; lab-confirmed COVID	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04318444
NCT04363450	Randomized, double blind, parallel assignment (USA)	HCQ	Placebo	Health care worker at risk ≥ 18 y/o (1,700)	Incidence of symptomatic COVID 19 & (+) SARS-CoV- 2	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04363450
NCT04363827	Randomized, open label, parallel assignment (Italy)	HCQ	NA	Health care workers at risk or asympto-matic COVID 19 ≥18 y/o (2,300)	Proportion of subjects with symptoms ± (+) RT-PCR on NPS; proportion with (-) RT-PCR	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04363827
NCT04340349	Randomized, double blind, triple, parallel A assignment (Mexico)	HCQ + Bromhexine	Bromhexine	Health care worker at risk ≥18 y/o (100)	(-) RT-PCR & serology for SARS-CoV-2 infection	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04340349
NCT04341441	Randomized, triple, parallel assignment (USA)	HCQ	Placebo	Health care workers & front liners at risk for COVID 19 18-75 y/o (3,000)	Decrease in rate of SARS CoV-2 infection & clinical COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341441
NCT04370015	Randomized, quadruple, parallel assignment	HCQ	Placebo	Health care workers at risk 18 - 60y/o	(-) RT PCR for SARS CoV-2; adverse	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04

	(Pakistan)			(374)	events			370015
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04330495	Randomized, double blind, parallel assignment (Spain)	HCQ	Placebo	COVID 19 18 - 75y/o (800)	Incidence of new COVID 19; mortality rate; ICU admission	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04370015
NCT04345159	Cohort Retrospective (France)	HCQ	NA	Autoimmune Disease on long term HCQ with or without COVID 19 ≥18y/o (1,500)	Odds Ratio measuring association between HCQ long term intake & history of COVID 19 Symptoms	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04345159
NCT04334967	Randomized, single, parallel assignment (USA)	HCQ	Vitamin C	COVID 19 ≥45 y/o (1,250)	% of patients hospitalized; % of patients who received mechanical ventilation	NA	Enrolling by Invitation	https://clinicaltrials.gov/ct2/show/NCT04334967
NCT04349228	Randomized, single, parallel assignment (Tunisia)	HCQ	NA	Health care workers at risk 18 - 65 y/o (530)	COVID 19 (+); viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04349228
NCT04332991	Randomized, quadruple, parallel assignment (USA)	HCQ	Placebo	Confirmed or suspected COVID 19 ≥ 18 y/o (510)	WHO Ordinal Scale on D15	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04332991
NCT04335084	Open Label single group assignment (USA)	HCQ + Vit C & D + Zinc; Vit C & D + Zinc	Placebo	Health care workers at risk COVID 19 ≥ 18 y/o	Prevention of COVID 19; adverse events	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04335084

				(600)				
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04352946	Randomized, quadruple, parallel assignment (USA)	HCQ	Placebo	Health care workers at risk ≥18 y/o (374)	Incidence of symptomatic & asymptom-atic COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04352946
NCT04347889	Randomized, open label, parallel assignment (USA)	HCQ	Vit C	Health care workers at risk ≥18 y/o (1,212)	% of health care worker who develop antibodies to SARS CoV-2	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04347889
NCT04326725	Observation-al Prospective (Turkey)	HCQ	Vitamins + Zinc	Health care workers at risk 20-90 y/o (80)	Protection against COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04326725
NCT04330586	Randomized, open label, parallel assignment (Korea)	Ciclesonide	Ciclesonide + HCQ	Mild COVID 18-80 y/o (141)	Rate of SARS CoV-2 eradication at D14	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04330586
NCT04374942	Randomized, quadruple, parallel assignment (Canada)	HCQ	Placebo	Health care workers at risk ≥18y/o (988)	COVID 19 (+) with detection of viral RNA, or sero-conversion	NA	Enrolling by Invitation	https://clinicaltrials.gov/ct2/show/NCT04374942
NCT04371523	Randomized, quadruple, parallel assignment (Canada)	HCQ	Placebo	Health Care Workers at risk ≥18 y/o (1,100)	# of health care worker tested (+) for SARS CoV-2	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04371523
NCT04333654	Randomized, quadruple, parallel assignment (USA, France,	HCQ	Placebo	COVID 19 ≥ 18 y/o (210)	Change in viral load in NPS for SARS CoV-2	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04333654

	Netherlands)							
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04341493	Randomized, single, parallel assignment (Mexico)	HCQ	Nitazoxanide + HCQ	COVID 19 ≥ 5y/o (86)	% of patients that required mechanical ventilation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341493
NCT04325893	Randomized, double blind, parallel assignment (France)	HCQ	Placebo	COVID 19 with chest CT suggesting pneumonia ≥ 75 y/o (1,300)	# of death from any cause or need for mechanical ventilation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04325893
NCT04350684	Randomized, triple, parallel assignment (Iran)	Umifenovir + IFN β 1a + LPV/r + HCQ	Umifenovir	COVID 19 ≥18 y/o (40)	Time to clinical improvement or discharge from hospital	NA	Enrolling by Invitation	https://clinicaltrials.gov/ct2/show/NCT04350684
NCT04347980	Randomized, single, parallel assignment (France)	CS + HCQ	HCQ	COVID 19 by RT PCR &/or CT > 18 y/o (122)	Mortality rate evaluated at D28	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04347980
NCT04351516	Randomized, quadruple, parallel assignment (Germany)	HCQ	Placebo	Mild to moderate COVID 19 ≥ 65 y/o (350)	Rate of hospital stay or death	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04351516
NCT04329611	Randomized, triple, single group assignment (Canada)	HCQ	NA	COVID 19 ≥ 18y/o (1,660)	Composite of hospital stay; mechanical ventilation or death	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329611
NCT04353037	Randomized, double blind, parallel assignment (USA)	HCQ	Placebo	Mild COVID 19; health care workers at risk 50-75y/o	Rate of hospital stay; rate of COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04353037

				(850)				
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04370262	Randomized, triple, parallel assignment (USA)	HCQ + Famotidine	HCQ	COVID 19 ≥18y/o (1,170)	Mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04370262
NCT04346147	Randomized, open label, parallel assignment (Spain)	HCQ + LPV/r; HCQ + Imatinib; HCQ + Baricitinib	LPV/r; Imatinib; Bricitinib	COVID 19 with pneumonia ECG QT < 0.4 ≥18 y/o (165)	Time to clinical improvement by 2 points on 7-category ordinary scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04346147
NCT04379492	Randomized, double blind, parallel assignment (USA)	HCQ	Placebo	COVID 19 ≥18y/o (120)	Clinical improvement on Ordinal Scale for Clinical Improvement (OSCI); # of patients requiring mechanical ventilation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04379492
NCT04336748	Randomized, triple, parallel assignment (Austria)	HCQ	placebo	Health care workers at risk ≥18 y/o (440)	Symptomatic or asympto-matic COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04336748
NCT04342169	Randomized, open label, parallel assignment (USA)	HCQ	Standard care	Within 48 hours (+) SARS CoV-2 ≥18 y/o (400)	Duration of viral shedding	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04342169
NCT04334928	Randomized, double blind, parallel assignment (Spain)	HCQ; Tenofovir/ Emtricitabine; HCQ + Tenofovir/ Emtricitabine	Placebo	Asymptoma-tic health care workers 18 – 70y/o (4,000)	# of confirmed symptomatic COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04334928

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04303299	Randomized, open label, parallel assignment (Thailand)	Oseltamivir + CQ;Darunavir / ritonavir + oseltamivir; LPV/r + Oseltamivir; Favipiravir + LPV/r;Darunavir /ritonavir + Oseltamivir + CQ; Darunavir /ritonavir + Favipiravir + CQ	Conventional quarantine	COVID 19 16 -100y/o (320)	SARS-CoV-2 eradication time	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04303299
NCT04319900	Randomized double blind, parallel assignment (China)	CQ + Favipiravir; Flavipiravir	Placebo	COVID 19 18-75y/o (150)	# of days of virus shedding; frequency of Improvement or recovery of respiratory symptoms	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04319900
ChiCTR2000030718	Randomized open label, parallel assignment (China)	CQ	Standard care	COVID 19 >18y/o (80)	Time to clinical recovery	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=50843
ChiCTR2000029988	Randomized, open label, parallel assignment (China)	CQ	Standard care	COVID 19 18 - 70y/o (80)	Time to clinical recovery	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49218
ChiCTR2000029939	Randomized Single blind parallel assignment (China)	CQ	Standard care	COVID 19 ≥18y/o (100)	Length of hospital stay	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49612

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000029935	Case series (China)	CQ	NA	COVID 19 (100)	Length of hospital stay	NA	Recruiting	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029935
ChiCTR2000029542	Non-randomized, cohort study (China)	CQ	Standard care	COVID 19 18 -80y/o (20)	viral (-) transforming time; cause-specific mortality	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=48968
NCT04316377	Randomized, open label, 2 arm, parallel assignment (Norway)	HCQ; CQ	Standard care	Moderate – severe COVID 19 ≥18y/o (202)	Rate of decline in SARS-CoV-2 viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04316377
NCT04303507	Randomized, double, parallel assignment (England)	HCQ; CQ	Placebo	COVID 19 with acute respiratory illness ≥16y/o (40,000)	# of symptomatic COVID 19; symptom severity of COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04303507
NCT04362332	Randomized, Open label, parallel assignment (Netherland)	HCQ	CQ	Moderate-severe COVID 19 18-110y/o (950)	Disease progression; ICU admission; death	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04362332
NCT04360759	Randomized, open label, parallel assignment (South Africa)	CQ; HCQ	Standard Care	Suspected or confirmed COVID 19 outpatient ≥ 18 y/o (560)	Event-free survival at 28 days	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04360759
NCT04351191	Randomized, quadruple, parallel assignment (Pakistan)	HCQ; CQ	Placebo	COVID 19 20 – 50y/o (400)	% of patients who become RT-PCR (-) for SARSCoV-2	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04351191

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04344779 8	Observation-al Prospective (Canada)	HCQ; CQ	HCQ/CQ +/- other DMARD + anti TNF or anti IL6 or JAK inhibitor or anti IL17	Arthritis patients on biologic & antimalarial drugs ≥18y/o (500)	# of patients developing signs and symptoms of COVID 19	NA	Enrolling by Invitation	https://clinicaltrials.gov/ct2/show/NCT04347798
NCT04346667	Randomized, double blind, parallel assignment (Pakistan)	HCQ CQ	Placebo	COVID 19 20-50 y/o (400)	% of patients who become RT-PCR (-) for SARS CoV-2	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04346667

Appendix 5. Azithromycin ± Hydroxychloroquine (HCQ) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Geleris J et al	Observation-al, prospective (USA)	HCQ ± Statin or ACEi or ARB or CS or Anticoagulant or Azithromycin or Remdesivir or Tocilizumab	Statin; ACEi or ARB; CS; Anticoagulant Azithromycin; Remdesivir; Tocilizumab	Hospitalized COVID 19 Adults (1,376)	Intubation or Death	No significant association between HCQ use & intubation or death.	Published	https://www.nejm.org/doi/full/10.1056/NEJMoa2012410?query=RP
Gautret P, et al.	Non-randomized, open label, parallel assignment (France)	HCQ; HCQ + Azithromycin	Standard care	Hospitalized COVID 19 patients >12 y/o (36)	Viral clearance at D6 post inclusion	Viral clearance at D6: HCQ + Azithromycin (100%); HCQ (57%); Control (12.5%). Effect is reinforced by Azithromycin.	Published	https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Lane J, et al	Cohort studies; self-controlled case series (Germany, Japan, Netherlands, Spain, UK, USA)	HCQ + Azithromycin	Sulfasalazine + Amoxicillin	Rheumatoid arthritis patients ≥18y/o (1,941,802)	Intention to treat & risk of SAEs associated with short-term use	Addition of Azithromycin: - prolonged hospital stay - heart failure & cardio-vascular mortality (synergistic effects on QT length)	Pre-print not peer reviewed	https://doi.org/10.1101/2020.04.08.20054551
Chorin E, et al.	Observation-al retrospective (USA)	HCQ + Azithromycin	None	COVID-19 >18 y/o (84)	Change in QT interval	Prolonged QTc (11%)	Completed	https://doi.org/10.1101/2020.04.02.20047050
Molina JM, et al.	Observation-al, prospective (France)	HCQ + Azithromycin	NA	Severe COVID-19 Adults (11)	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
Gautret P, et al.	Observation-al, prospective (France)	HCQ + Azithromycin	NA	COVID-19 >18 y/o (80)	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.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04321278	Randomized, open label, parallel assignment (Israel)	HCQ + Azithromycin	HCQ	Probable or confirmed COVID 19 ≥18y/o (440)	Evaluation of clinical status	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04321278
NCT04322396	Randomized, Double blind, quadruple, parallel assignment (Denmark)	HCQ + Azithromycin;	Placebo	COVID 19 ≥18y/o (226)	# of days alive & discharged from hospital within 14 days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04322396
NCT04322123	Randomized, Open label, parallel assignment (Israel)	HCQ; HCQ + Azithromycin	Standard care	Suspected or confirmed COVID 19 ≥18y/o (630)	Evaluation of clinical status	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04322123
NCT04324463	Randomized, open label; parallel assignment (Canada)	HCQ or CQ + Azithromycin; HCQ or CQ + Azithromycin + IFN β; IFN β	Standard care	COVID 19 ≥18y/o (1,500)	Hospital admission; invasive mechanical ventilation or mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324463
NCT04329832	Randomized, open label parallel assignment (USA)	HCQ	Azithromycin	Admitted COVID 19 ≥18y/o (300)	COVID Ordinal Outcomes Scale at D14; hospital & ventilator-free days at 28 days	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329832?term=azithromycin&recrs=adf&cond=covid+19&draw=2&rank=1
NCT04334382	Non-randomized, open label, parallel assignment (USA)	HCQ	Azithromycin	COVID 19 ≥45y/o (1,550)	Hospitaliz-ation within 14 days of enrollment; duration of COVID 19 symptoms	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04334382?term=azithromycin&recrs=adf&cond=covid+19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04354597	Randomized, open label, parallel assignment (Jordan)	HCQ + Azithromycin	NA	Health care workers at risk (200)	Effect in preventing COVID 19 with (-) RT-PCR on NPS	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04354597
NCT04370782	Randomized, open label, parallel assignment (USA)	HCQ	Zinc + Azithromycin + Doxycy-cline	Outpatient COVID 19 ≥30 y/o (750)	Time to resolution of symptoms	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04370782
NCT04329832	Randomized, open label, parallel assignment (USA)	HCQ	Azithromycin	Hospitalized COVID or suspected COVID 19 ≥18y/o (300)	COVID Ordinal Outcomes Scale at D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329832
NCT04371406	Randomized, open label, parallel assignment (France)	HCQ + Azithromycin	Zinc	Early-Stage disease in COVID 19 18-75 y/o (2,770)	Rate of patients with unfavorable outcome: -hospitalize-tion -death -O2 sat ≤ 92%; viral load by NPS	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04371406
NCT04365231	Randomized, open label, parallel assignment (France)	HCQ + Azithromycin	Standard care	Pregnant women with mild COVID 19 ≥18y/o (50)	% Patients with (-) RT-PCR on NPS at D7	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04365231
NCT04374903	Randomized, open label, parallel assignment (Jordan)	HCQ & Azithromycin	HCQ + Sirolimus	COVID 19 ≥18y/o (58)	Time to Clinical Improvement	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04374903

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04345862	Randomized, Double blind, parallel assignment (France)	HCQ	HCQ + Azithromycin	Admitted COVID 19 pneumonia Adults (150)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04345861
NCT04345862	Randomized, Double blind, parallel assignment (France)	HCQ	HCQ + Azithromycin	Admitted COVID 19 pneumonia Adults (150)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04345861
NCT04359953	Randomized, open label, parallel assignment (France)	HCQ	Azithromycin + Telmisartan	COVID 19 ≥60 y/o (1,600)	2-week survival rate	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359953
NCT4332094	Randomized, open label, parallel assignment (Spain)	HCQ + Azithromycin + Tocilizumab	HCQ + Azithromycin	COVID 19 ≥18 y/o (276)	In-hospital mortality; need for mechanical ventilation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04332094
NCT04348474	Open label, single group assignment (Brazil)	HCQ	Azithromycin	COVID 19 with mild ARDS ≥18 y/o (200)	Change in clinical condition (7 points ordinal scale)	NA	Suspended	https://clinicaltrials.gov/ct2/show/NCT04348474
NCT04329572	Non-randomized, open label, single group assignment (Brazil)	HCQ	Azithromycin	Moderate-severe COVID 19 with Pneumonia ≥18 y/o (400)	Evolution of acute respiratory syndrome	NA	Suspended	https://clinicaltrials.gov/ct2/show/NCT04329572
NCT04358068	Randomized, double blind, parallel assignment (USA)	HCQ	Azithromycin	COVID 19 with severe ARDS ≥18 y/o (2,000)	Proportion of patients from any cause	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04358068

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04336332	Randomized, open label, parallel assignment (USA)	HCQ	HCQ + Azithromycin	COVID 19 18 - 69y/o (160)	Changes in viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04336332
NCT04344457	Open label, single group assignment (USA)	HCQ + Indomethacin + Azithromycin	NA	COVID 19 ≥ 18y/o (80)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04344457
NCT04347512	Randomized, open label, parallel assignment (France)	HCQ + Azithromycin	Standard Care	COVID 19 with pneumonia ≥18 y/o (405)	Rate of patients with significant hypoxemia	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04347512
NCT4335552	Randomized, open label, factorial assignment (USA)	HCQ	Azithromycin	COVID 19 suspects with pneumonia ≥12 y/o (500)	WHO Ordinal scale at D14 days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04335552
NCT04341870	Randomized, open label, parallel assignment (France)	Sarilumab + Azithromycin + HCQ	Sarilumab	Moderate to severe COVID 19 Adult (27)	Need for ventilation, intensive care or death	NA	Suspended	https://clinicaltrials.gov/ct2/show/NCT04341870
NCT04361461	Randomized, open label, parallel assignment (Brazil)	HCQ	HCQ + Azithromycin	Moderate-severe confirmed or suspected COVID 19 ≥18y/o (500)	WHO Ordinal scale from basal to D14	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04361461
NCT04345861	Randomize, double blind, parallel assignment (France)	HCQ + Azithromycin	HCQ	COVID 19 with pneumonia (150)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04345861

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04321278	Randomized, open label, parallel assignment (Brazil)	HCQ + Azithromycin	HCQ	Probable or confirmed COVID 19 ≥18y/o (440)	Evaluation of clinical status on D15	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04321278
NCT04358081	Randomized, Double blind, quadruple, parallel assignment (USA)	HCQ	HCQ + Azithromycin	Moderate-Severe COVID 19 with Pneumonia ≥ 18 y/o (444)	% of participants who achieve clinical response at D15	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04358081
NCT04322396	Randomized, quadruple, parallel assignment (Denmark)	HCQ + Azithromycin	Standard care	COVID 19 >18 y/o (226)	# of days alive & discharged from hospital	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04322396
NCT04338698	Randomized, double blind, parallel assignment (Pakistan)	HCQ	Oseltamivir + Azithromycin	COVID 19 ≥18 y/o (500)	Turning (-) for SARS Cov-2 on RT PCR	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04338698
NCT04359316	Randomized, triple, parallel assignment (Iran)	Azithromycin	HCQ	COVID 19 ≥ 18 y/o (40)	Clinical improvement; discharge from hospital	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359316
NCT04343092	Randomized, double blind, parallel assignment (Iraq)	Ivermectin + HCQ + Azithromycin	HCQ + Azithromycin	COVID 19 with pneumonia > 18 y/o (50)	# of patients cured	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04343092
NCT04322123	Randomized, open label, parallel assignment (Brazil)	HCQ	HCQ + Azithromycin	Suspected of confirmed COVID 19 > 18 y/o (630)	Evaluation of clinical status of patients on D15	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04322123

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04341207	Non-randomized, open label, parallel assignment (France)	HCQ + Azithromycin	HCQ	Locally advanced & metastatic malignancy ≥ 18 y/o (1,000)	Prevalence & incidence of COVID 19 in cancer patients; disease-specific mortality rate in patients treated with HCQ & Azithromycin	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341207
NCT04344379	Randomized, double blind, parallel assignment (France)	HCQ	Azithromycin	Health care worker at risk ≥18y/o (900)	# of health care worker with (+) serology or RT-PCR for SARS CoV-2	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04344379
NCT04374552	Randomized, quadruple, parallel assignment (USA)	HCQ + Azithromycin	Placebo	Asymptoma-tic COVID 19 ≥20y/o (140)	Rate of decline in viral load	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04374552
NCT04371744	Observation-al Prospective (France)	HCQ + Azithromycin	NA	Ambulatory COVID with smart-watches application > 18 y/o (100)	Corrected QTc interval measurement using artificial intelligence-based ECG via smart watches vs 12 lead ECG	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04371744
Nct04341727	Randomized, open label, parallel assignment (USA)	HCQ	HCQ + Azithromycin; CQ + Azithromycin	Hospitalized COVID 19 ≥ 18 y/o (500)	Hours to recovery	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341727

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04353245	Observational Prospective (Brazil)	HCQ + Azithromycin	NA	COVID 19 ≥18 y/o (130)	Fibrosis; decreased ergospirometry functional capacity	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04353245
NCT04339426	Non-randomized, open label, single group assignment (USA)	Azithromycin +Atovaquone	NA	COVID 19 18 – 95y/o (25)	Virology cure rate; incidence of adverse effects; cardiac toxicity	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04339426?term=azithromycin&recrs=adf&cond=covid+19&draw=2&rank=2

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

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Sciascia S et al.	Prospective open label, single-arm (Italy)	Tocilizumab	NA	Severe COVID 19 50 -74y/o (63)	Improvement in clinical & laboratory parameters	Use of tocilizumab within 6 days from admission was associated with increased likelihood of survival	Published	https://www.clinexprheumatol.org/article.asp?a=15723
Xu et al.	Observational, prospective (China)	Tocilizumab + Lopinavir + Methylprednisolone	NA	Severe or critical COVID-19 (21)	Normalization of body temperature, O2 sat & improvement in CT scan findings	After day 1 of Tocilizumab: normal temperature; improved SpO_2 & resolution of lung opacities	Completed	http://www.chinaxiv.org/abs/202003.00026

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04320615	Randomized, double-blind, Parallel assignment (Switzerland)	Tocilizumab	Placebo	COVID-19 Pneumonia ≥18y/o (330)	Clinical status using a 7-Category Ordinal Scale	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04320615
NCT04317092	observational cohort, open label, single arm assignment (Italy)	Tocilizumab	NA	COVID-19 Pneumonia (400)	One-month mortality rate	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04317092
NCT04306705	Observation-al cohort (China)	Tocilizumab	Continuous renal replacement therapy, standard care	Severe COVID-19 with CRS 18-80 y/o (120)	Proportion of patients with normalization of fever & O2 sat through D14	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04306705
NCT04331795	Non-randomized, open-label single group assignment (USA)	Tocilizumab low dose; Tocilizumab high dose	NA	Patients with COVID 19 & radiographic evidence of infiltrates ≥18y/o (50)	Clinical & biochemical responses	NA	Recruiting	https://clinicaltrials.gov/show/NCT04331795
ChiCTR2000029765	Randomized, Open label, parallel assignment (China)	Tocilizumab	Standard care	COVID-19 with severe pneumonia & elevated IL-6 18 – 85y/o (188)	Cure rate	None	Recruiting	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000029765
NCT04315480	Simon's 2 stages optimal design, single arm, open Label (Italy)	Tocilizumab	NA	COVID Pneumonia needing O2 support <18 & >90y/o (38)	Arrest in deterioration of pulmonary function, improving pulmonary function	NA	Active, not recruiting	https://ClinicalTrials.gov/show/NCT04315480

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04310228	Randomized, open label, parallel assignment (China)	Tocilizumab + Favipiravir	Tocilizumab; Favipiravir	COVID-19 with elevated IL-6 18-65 y/o (150)	Clinical cure rate	NA	Recruiting	https://ClinicalTrials.gov/show/NCT04310228
NCT04332913	Observation-al, cohort (Italy)	Tocilizumab	NA	COVID-19 pneumonia ≥18 y/o (30)	% of patients with complete recovery (fever lysis, normal SpO2 D14 of treatment	NA	Recruiting	https://clinicaltrials.gov/show/NCT04332913
ChiCTR2000030196	Case series (China)	Tocilizumab	NA	COVID-19 with elevated IL 6 (60)	Relief of Cytokine Release Syndrome	NA	Pending	http://www.chictr.org.cn/showprojen.aspx?proj=49883
NCT04333914	Randomized, cohort (France) Open label, parallel assignment (France)	CQ analog; Nivolumab; Tocilizumab	Standard care	COVID-19 w/ advanced or metastatic hematologi-cal or solid tumor ≥18y/o (273)	28-day survival rate	NA	Recruiting	https://clinicaltrials.gov/show/NCT04333914
NCT04331808	Randomized, open label, parallel assignment (France)	Tocilizumab	Standard care	COVID 19 moderate - severe pneumopathy ≥18 y/o (240)	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, open label. Parallel assignment (USA)	Tocilizumab + Pembro-lizumab	Standard care	COVID 19 w/ with ARDS not responsive to 1st line tx ≥18 y/o (24)	% of patients with normalization of SpO2 ≥96%	NA	Not yet recruiting	https://clinicaltrials.gov/show/NCT04335305

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04335071	Randomized, double blind, quadruple, parallel assignment (Switzerland)	Tocilizumab	Placebo	COVID 19 with pneumonia 30 – 80y/o (100)	# of patients with ICU admission, intubation or death	NA	Not yet recruiting	https://clinicaltrials.gov/show/NCT04335071
NCT04363736	Randomized, open label, parallel assignment (USA)	Tocilizumab high dose	Tocilizumab low dose	Moderate to severe COVID-19 pneumonia ≥18y/o (100)	CRP level	NA	Not yet recruiting	www.clinicaltrials.gov/ct2/show/study/NCT04363736
NCT04363853	Single-arm, open-label (Mexico)	Tocilizumab	NA	Patients with severe or critical COVID 19 18 – 90y/o (200)	After Removal of mechanical ventilation: - hematic biometry - blood chemistry - blood gas - thorax radiography	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04363853
NCT04361552	Randomized, open label parallel assignment (USA)	Tocilizumab	Standard care	Hospitalized COVID 19 patients with co-morbidities ≥18y/o (180)	7-day length of invasive mechanical ventilation; 30-day mortality rate	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04361552
NCT04361032	Randomized, open label parallel assignment (Tunisia)	Tocilizumab	Defer ox-amine	COVID-19 admitted in ICU ≥18 -	Mortality rate	NA	Not yet recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04361032

				80y/o (260)				
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04359667	Observational, prospective (Croatia)	Tocilizumab	NA	Severe COVID-19 pneumonia ≥ 18 (30)	Serum IL-6 & soluble IL-6 receptor for clinical outcomes in severe COVID-19	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/record/NCT04359667
NCT04356937	Randomized, double blinded, parallel assignment (USA)	Tocilizumab	Placebo	severe COVID-19, non-ICU, 19 – 79 y/o (300)	Proportion of patients requiring mechanical ventilation	NA	Not yet recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04356937
NCT04346355	Randomized, open label, parallel, assignment (Italy)	Tocilizumab	Standard care	COVID 19 patients with pneumonia (398)	Entry into ICU with mechanical ventilation or death	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04346355
NCT04345445	Randomized, open-label, cross-over assignment (Malaysia)	Tocilizumab	Methylpred-nisolone	Hospitalised COVID-19, >18y/o (310)	Proportion of patients requiring mechanical ventilation; mean days of ventilation	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04345445
NCT04322773	Randomized, open label, sequential assignment (Denmark)	Tocilizumab low dose; Tocilizumab high dose; Sarilumab	Standard care	COVID-19 with pneumonia needing O2 support (200)	Time to independ-ence from O2 therapy	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04322773
NCT04322188	Observational, cohort	Siltuximab	NA	COVID 19 with ARDS	Reduction of need for	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04322

	(Italy)			≥18 y/o (50)	invasive ventilation; 30-day mortality			188
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04329650	Randomized, open label, Parallel assignment (Spain)	Siltuximab + Methylpred-nisolone + LPV/r	Methylpred-nisolone	COVID 19 patients with pneumonia ≥18 y/o (200)	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
NCT04315298	Randomized, double blind, quadruple, parallel assignment (USA)	Sarilumab low dose; Sarilumab low dose	Placebo	Severe COVID-19 with pneumonia ≥18 y/o (400)	% change in CRP level; time to improvement in clinical status	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04315298
NCT04327388	Randomized, quadruple, parallel assignment (USA)	Sarilumab	Placebo	Severe COVID-19 with pneumonia ≥18 yo (300)	Time to lysis of fever for 48 hrs or until discharge; % of patients reporting each severity rating	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04327388
NCT04357808	Randomized, open label, Parallel assignment (Spain)	Sarilumab	Standard care	Moderate to severe COVID 19 >18y/o (30)	Mean change clinical status assessment (7-pt ordinal scale at D7); duration of hospital stay; death	NA	recruiting	https://www.clinicaltrials.gov/ct2/show/record/NCT04357808
NCT04341870	Randomized, open label, parallel	Sarilumab + Azithromycin + HCQ	Sarilumab	COVID 19 with moderate -	Need for ventilation admission to	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/re

	assignment (France)			severe pneumonia 18 – 80y/o (60)	ICU; death			cord/NCT04341870
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
CT04357860	Randomized, open label, parallel assignment (Spain)	Sarilumab 200 mg; Sarilumab 400 mg	Standard care	COVID-19 with pneumonia at risk of ARDS 18 – 75y/o (120)	Ventilation requirements at D28 or when the subject is discharged	NA	Not yet recruiting	https://www.clinicaltrials.gov/ct2/show/record/NCT04357860
NCT04359901	Randomized open label, play-the-winner-design (USA)	Sarilumab	standard care	moderate COVID19 ≥18y/o (120)	intubation or death within 14 days	NA	recruiting	https://www.clinicaltrials.gov/ct2/show/study/NCT04359901
NCT04345289	Randomized, quadruple, parallel assignment (Denmark)	Sarilumab; Baricitinib; HCQ; CP	Placebo	COVID-19 with pneumonia ≥18y/o (1,500)	All-cause mortality; need of invasive mechanical ventilation	NA	Not yet recruiting	https://www.clinicaltrials.gov/ct2/show/study/NCT04345289

Appendix 7. Anti-IL1 Studies for COVID 19: Anakinra and Canakinumab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Aouba A, et al.	Prospective case series (France)	Anakinra	N/A	Moderate to severe COVID-19 pneumonia at high risk of worsening >18 y/o	Avoidance of mechanical ventilation	1 patient developed acute respiratory failure after 1 dose; the 8 other patients	Published	https://ard.bmj.com/content/annrheumdis/early/2020/05/05/annrheumdis-2020-217706.full.p

				(9)		had good clinical & biologic outcomes		df
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04357366	Open label, single group assignment (Greece)	Anakinra + trimethoprim/ sulfamethoxazole	N/A	COVID-19 patients ≥18 y/o (100)	Ratio of patients who will not develop serious respiratory failure	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04357366?term=Anakinra&cond=COVID-19&draw=2&rank=1
NCT04324021	Randomized, open label, 3 arm, parallel assignment (Italy)	Anakinra; Emapalumab	Standard care	Patients with COVID 19 30 - 79 y/o (54)	Proportion of patients not requiring mechanical ventilation or ECMO	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324021?term=Anakinra&cond=COVID-19&draw=2&rank=2
NCT04330638	Randomized, open label, factorial assignment (Belgium)	Anakinra; Siltuximab; Anakinra + Siltuximab + Tocilizumab; Anakinra + Tocilizumab	Standard care	Patients with COVID 19 8 - 80 y/o (342)	Time to clinical improvement	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330638?term=Anakinra&cond=COVID-19&draw=2&rank=5
NCT04339712	Non-randomized, open-label, factorial assignment (Greece)	Anakinra for macrophage activation syndrome	Tocilizumab for immune dysregulation	COVID-19 patients ≥18 y/o (40)	Change of baseline total sequential organ failure assessment score; improving lung involvement measure-	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04339712?term=Anakinra&cond=COVID-19&draw=2&rank=3

					ments; increase of pO2/FiO2 ratio			
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04362111	Randomized, triple-blinded, parallel assignment (USA)	Anakinra	Normal saline	COVID-19 patients ≥18 y/o (40)	Improvement in cytokine storm markers; no requirement for mechanical ventilation	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04362111?term=Anakinra&cond=COVID-19&draw=2&rank=4
NCT04341584	Randomized, open-label, parallel assignment (France)	Anakinra	Standard care	Patients with COVID-19 > 18 y/o nested in the CORIMUNO-ANA study (240)	• Survival w/o ventilator at D14; • WHO progression scale ≤ 5	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04341584?term=Anakinra&cond=COVID-19&draw=2&rank=6
NCT02735707	Randomized, open-label, factorial assignment (New Zealand)	Anakinra; Interferon-β1a	N/A	Patients with suspected or proven COVID19 >18 y/o (7,100)	All-cause mortality; days alive; outside of ICU	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT02735707?term=Anakinra&cond=COVID-19&draw=2&rank=7
NCT04366232	Randomized, open-label, parallel assignment (France)	Anakinra; Anakinra + Ruxolitinib	Standard care	COVID-19 patients >18 y/o, either in Stage 2b or 3 (50)	Biological criteria (refer to source for details)	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04366232?term=Anakinra&cond=COVID-19&draw=2&rank=1
NCT04364009	Randomized, open-label,	Anakinra	Standard care	COVID-19 patients	Patient alive, not requiring	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/sh

	parallel assignment (France)			>18 y/o (240)	mechanical ventilation or ECMO			ow/NCT04364009?term=Anakinra&cond=COVID-19&draw=2&rank=2
Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04362943	Retrospective observational study (Spain)	Anakinra; Baricitinib	N/A	COVID-19 patients >70 y/o (576)	Mortality	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04362943?term=Anakinra&cond=COVID-19&draw=2&rank=3
NCT04348448	Observation-al cohort (Italy)	Canakinu-mab	N/A	Patients with COVID-19 pneumonia >18 y/o (100)	% of patients not requiring ICU admission	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04348448?term=Canakinumab&cond=COVID-19&draw=2&rank=1
NCT04362813	Randomized, double-blind, parallel assignment (France)	Canakinu-mab	Placebo (5% dextrose)	Patients with severe COVID-19 pneumonia >18 y/o (450)	# of patients with clinical response	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04362813?term=Canakinumab&cond=COVID-19&draw=2&rank=1
NCT04365153	Randomized, quadruple-blind, factorial assignment (USA)	Canakinu-mab 600 mg Canakinu-mab 300 mg	Placebo	Patients with COVID-19 >18 y/o (45)	Time to clinical improvement up to day 14	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04365153?term=Canakinumab&cond=COVID-19&draw=2&rank=3

Appendix 8. IL 2 Study for COVID 19: Aldesleukin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04357444	Randomized, quadruple, parallel assignment (France)	Low dose IL-2	Placebo	COVID 19 >18y/o (30)	PaO2/FiO2 ratio at D7	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04357444

Appendix 9. Anti-TNF Study for COVID: Adalimumab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
ChiCTR2000030089	Randomized, open-label, parallel assignment (China)	Adalimumab	Standard care	Severe & critical COVID 19 ≥18y/o (60)	Time to clinical improvement	NA	Not yet recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=49889

Appendix 10. Anti-GM-CSF Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04351152	Randomized, double blind, parallel assignment (USA)	Lenzilumab	Standard care	COVID 19 patients 18 – 85y/o (238)	Incidence of invasive mechanical ventilation and/or mortality	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04351152?term=GM+CSF&cond=COVID&draw=2&rank=3&view=record
NCT04341116	Randomized, quadruple, parallel assignment (USA)	TJ003234	Placebo	COVID 19 patients ≥18 y/o (144)	Proportion of subjects experiencing deterioration in clinical status	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04341116?term=GM+CSF&cond=COVID&draw=2&rank=4

Appendix 11. JAK 1 and 2 Inhibitors Studies for COVID: Baricitinib and Ruxolitinib

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04340232	Interventional open label, single group assignment (USA)	Baricitinib	Standard care	COVID 19 patients with pneumonia 18 – 89y/o (80)	Disease severity on 8-point ordinal scale at D15; blood test results; adverse events	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04340232?term=Baricitinib+for+COVID&draw=2&rank=1
NCT04358614	Non-randomized, open label, cross over assignment (Italy)	Baricitinib	Standard care	COVID 19 with pneumonia 18 – 85y/o (12)	safety of Baricitinib combined with LPV/r	NA	Recruitment Completed	https://clinicaltrials.gov/ct2/show/NCT04358614?cond=Baricitinib+for+COVID+19&draw=2&rank=2
NCT04320277	Non-randomized, open label, crossover assignment (Italy)	Baricitinib + LPV/r	Antiviral + HCQ	Mild to moderate COVID 19 18 – 85y/o (200)	% of patients transfer to ICU	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04320277?term=baricitinib&draw=3&rank=14
NCT04373044	Open label, single group assignment (USA)	Baricitinib + HCQ + LPV/r + Remdesivir	NA	COVID 19 ≥18y/o (59)	reduction of proportion of patients requiring mechanical ventilation or dying	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04373044?cond=Baricitinib+for+COVID+19&draw=2&rank=4
NCT04321993	Non-randomized, open label, parallel assignment (Canada)	Baricitinib; LPV/r; HCQ	Standard care	Hospitalized moderate to severe COVID 19 ≥18 y/o (1,000)	Clinical status of subjects at D15 (on a 7-point ordinal scale)	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04321993?term=baricitinib&draw=1&rank=62

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04346147	Randomized, open label, parallel assignment (Spain)	HCQ + LPV/r; HCQ + Imatinib; HCQ + Baricitinib	HCQ	COVID 19 pneumonia ≥18y/o (165)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04346147?cond=Baricitinib+for+COVID+19&draw=2&rank=4
NCT04348071	Open label, single group assignment (USA)	Ruxolitinib	NA	COVID 19 patients with oneumonia 18 89y/o (80)	Disease severity; blood test results; incidence of AE	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04348071?cond=ruxolitinib+for+COVID+19&draw=2&rank=1
NCT04355793	Open label expanded access program (USA)	Ruxolitinib	NA	COVID 19 patients with respiratory distress ≥12y/o	NA	NA	Available	https://clinicaltrials.gov/ct2/show/NCT04355793?cond=ruxolitinib+for+COVID+19&draw=2&rank=2
NCT04362137	Randomized, double blind, parallel assignment (USA)	Ruxolitinib	Placebo	COVID 19 with pneumonia ≥12y/o (402)	Proportion of death, respiratory failure or ICU care	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04362137?cond=ruxolitinib+for+COVID+19&draw=2&rank=3
NCT04354714	Open label, single group assignment (USA)	Ruxolitinib	NA	COVID 19 patients with pneumonia ≥18y/o (25)	Overall survival	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04354714?cond=ruxolitinib+for+COVID+19&draw=2&rank=4
NCT04337359	Cohort study, Managed Sccess Program (USA)	Ruxolitinib	NA	Patients with severe & very severe COVID 19 ≥6y/o	NA	NA	Available	https://clinicaltrials.gov/ct2/show/NCT04337359?cond=ruxolitinib+for+COVID+19&draw=2&rank=5
NCT04361903	Observation-al cohort (Italy)	Ruxolitinib	NA	Severe COVID 19 ≥18y/o (13)	# of patients who avoid mechanical ventilation in ARDS in COVID-19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04361903?cond=ruxolitinib+for+COVID+19&draw=2&rank=6

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04334044	Open label, Single group assignment (Mexico)	Ruxolitinib	NA	COVID 19 with ARDS ≥18y/o (20)	Recovery of pneumonia	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04334044?cond=ruxolitinib+for+COVID+19&draw=2&rank=7
NCT04331665	Open label, single group assignment (Canada)	Ruxolitinib	NA	COVID 19 with pneumonia ≥12y/o (64)	Proportion of patients who become critically ill; # of AE	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04331665?cond=ruxolitinib+for+COVID+19&draw=2&rank=8
NCT04348695	Randomized, open label, parallel assignment (Spain)	Ruxolitinib	Standard care	COVID 19 ≥18y/o (94)	% of patients who develop severe respiratory failure	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04348695?cond=ruxolitinib+for+COVID+19&draw=2&rank=9
NCT04359290	Open label, single group assignment (Germany)	Ruxolitinib	NA	COVID 19 ARDS ≥18y/o (15)	Overall survival	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359290?cond=ruxolitinib+for+COVID+19&draw=2&rank=10
NCT04338958	Non-randomized, open label, single group (Germany)	Ruxolitinib	NA	COVID 19 ≥18y/o (200)	overall response rate in reversal of hyperinflammation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04338958?cond=ruxolitinib+for+COVID+19&draw=2&rank=11
NCT04366232	Randomized, open label, parallel assignment (France)	Anakinra; Anakinra + Ruxolitinib	Standard care	COVID 19 ≥18y/o (50)	Biological criteria	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04366232?cond=Ruxolitinib+for+COVID+19&draw=2&rank=5
NCT04377620	Randomized, double blind, parallel assignment (USA)	Ruxolitinib	Placebo	COVID 19 ≥18y/o (500)	Proportion of participants who have died due to any cause	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04377620?cond=Ruxolitinib+for+COVID+19&draw=1&rank=6

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04374149	Non-randomized, open label, sequential assignment (USA)	Ruxolitinib + Therapeutic plasma exchange (TPE)	TPE	12 – 80y/o (20)	Overall Response Rate	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04374149?cond=Ruxolitinib+for+COVID+19&draw=1&rank=11#contacts

Appendix 12. CCR5 Inhibitor Studies for COVID 19: Leronlimab

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04343651	Randomized, double blind, quadruple, Parallel assignment (USA)	Leronlimab	Placebo	Mild to moderate COVID 19 with respiratory disease ≥18 y/o (75)	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
NCT04347239	Randomized, double blind, quadruple, parallel assignment (USA)	Leronlimab	Placebo	Severe-critical COVID 19 ≥18 y/o (390)	All-cause mortality at D28	Preliminary/ secondary outcome mortality on day 14 is 18%	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04347239?cond=Leronlimab+for+COVID+19&draw=2&rank=2#contacts

Appendix 13. Interferons (IFNs) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Qiu et al.	Retrospective cohort study (China)	IFN α + LPV/r	NA	Mild-moderate COVID 19 0-16y/o (36)	Clinical presentation; diagnostic findings; therapy & outcome	Improvement in pneumonia at D4–10; (-) SARS-CoV-2 RT-PCR after a mean of 10 days; mean # of hospital days was 14 days	Published	https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930198-5
Zhou Q e al.	Non-randomized, retrospective (China)	IFN α-2B + Arbidol	IFN α-2B; Arbidol	COVID 19 Adults (77)	Clinical improvement	IFN-α 2b + arbidol reduced the duration of (+) SARS Cov-2 on NPS & of elevated IL-6 & CRP	Published	https://www.medrxiv.org/content/10.1101/2020.04.06.20042580v1.full.pdf+html
Hung IFN, et al.	Randomized, open-label, Parallel assignment (Hongkong)	LPV/r + Ribavirin + IFN β-1B	LPV/r	Hospitalized Patients with COVID 19 ≥18 y/o (127)	Time to negative NPS for SARS-Cov-2 viral RT-PCR	LPV/r + Ribavirin + IFN β1B were safe & superior to LPV/r in shortening virus shedding, alleviating symptoms & facilitating discharge of patients with mild to moderate COVID 19.	Published	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)
Chen Y, et al.	Open label single group assignment, (China)	Ganovo + Ritonavir ± IFN	NA	COVID-19 18 – 75y/o (11)	Rate of composite adverse outcome	NA	Completed	https://clinicaltrials.gov/ct2/show/study/NCT04291729?term=IFN+and+Covid-19&cond=covid-19&draw=3&rank=8
ChiCTR2000031196	Non-randomized, retrospective (China)	LPV/r + interferon α	Standard care	RT-PCR SARS-CoV-2 (+) 16 -85y/o (90)	Time of SARS-CoV-2 clearance	NA	Recruiting	http://www.chictr.org.cn/showprojen.aspx?proj=51112
NCT04293887	Randomized, open label, parallel assignment (China)	rh IFN α1β	Standard care	COVID-19 within 7 days onset of symptoms >18 y/o (328)	Incidence of side effects within 14 days of enrollment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04293887
NCT04344600	Randomized single-blind, parallel assignment (USA)	Peg-IFN ʎ1a	Placebo (Saline)	Non-hospitalized high risk for COVID 19 18-80 y/o (164)	Proportion of participants with no COVID 19; days to no (-) SARS-CoV-2	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04344600?cond=interferon+in+covid-19&draw=2&rank=10
NCT04350281	Randomized, open-label, parallel assignment (Hongkong)	Interferon β-1b + HCQ	HCQ	Hospitalized patients with COVID 19 ≥18 y/o (80)	Time to (-) NPS SARS-CoV-2 viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350281?cond=interferon+in+covid-19&draw=2&rank=9
NCT04320238	Non-randomized; open label, Parallel assignment (China)	Low risk: rh IFN α-1b; High risk: rh IFN α-1b + thymosin α1	None	Formally serving medical staff in Taipei Hospital 18 - 65 y/o (2,944)	New-onset COVID 19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04320238?cond=interferon+in+covid-19&draw=2&rank=8

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04254874	Randomized cohort, single, parallel assignment (China)	Arbidol + Peg-IFN α-2b	Arbidol	COVID 19 patients with pneumonia ≥18 y/0 (100)	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, open label. Parallel assignment (USA)	Peg-IFN ʎ	Standard care	Patients with COVID 16 ≥18 y/o (20)	(-) 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
NCT04350671	Randomized, double-blind, Triple, parallel assignment (Iran)	IFN β1a + LPV/r + HCQ	LPV/r + HCQ	COVID-19 by RT-PCR or CT Scan ≥ 50 y/o (40)	Time to clinical improvement	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04350671?cond=interferon+in+covid-19&draw=2&rank=2
NCT04343768	Randomized, open label, Parallel assignment (Iran)	HCQ + LPV/r IFN-β 1a; HCQ + LPV/r + IFN-β 1b	HCQ + LPV/r	COVID 19 with O2 sat ≤93% ≥ 18y/o (60)	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, Triple, Parallel assignment (Iran)	Umifenovir + IFN-β1a + LPV/r + HCQ	IFN-β1a + LPV/r + HCQ	COVID-19 time of onset of symptoms ≤10 days ≥18 y/o (40)	Time to clinical improvement	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04350684?cond=interferon+in+covid-19&draw=2&rank=6
NCT04254874	Randomized cohort, single, parallel assignment (China)	Abidol + Peg-IFN α-2b	Standard care + Abidol	COVID 19 by RT PCR & CT scan with pneumonia ≥18 y/o (100)	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, open label, parallel assignment (USA)	PegIFN ʎ	Standard care	COVID-19 ≥18 y/o with (20)	Negative COVID PCR testing D7 after treatment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04343976?cond=interferon+in+covid-19&draw=2&rank=3
NCT04354259	Randomized, open label, parallel assignment (Canada)	Peg- IFN ʎ	No specific therapy	COVID-19 18-70y/o (140)	Proportion of participants with (-) **SARS-CoV-2**; rate of severe AEs	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04354259?term=IFN+and+Covid-19&cond=covid-19&draw=3&rank=9
NCT04324463	Randomized, open-label, parallel group (Canada)	IFN β + Azithromycin + HCQ	IFN β	COVID-19 ≥18y/o (1,500)	Invasive mechanical ventilation or mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04324463?term=IFN+and+Covid-19&cond=covid-19&draw=3&rank=14
NCT04315948	Randomized, open labe, parallel assignment (France)	IFN β 1a	Standard care	COVID-19 ≥18y/o (3,100)	% of subjects reporting each severity rating	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04315948?term=IFN+and+Covid-19&cond=covid-19&draw=3&rank=17
NCT02735707	Randomized, open label, factorial assignment (REMAP-CAP)	Oseltamivir; LPV/r; HCQ + LPV/r; Ritonavir; IFN-B1a; Anakinra;CS; Tocilizumab; Sarilumab	Standard care; no anti-viral agent	Severe to critical suspected or confirmed COVID -19 >18y/o (7,100)	All-cause mortality (90 days); days alive & outside of ICU (21 days)	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT02735707?term=oseltamivir&cond=covid+19&draw=1&rank=8
NCT04324021	Randomized, open label, 3 arm, parallel assignment, 3-arm, (Sweden)	Anti-IFN γ + Anakinra	Standard care	Hospitalized COVID 19 with respiratory distress & hyperinflam-mation state 30 to 79 y/o (54)	Proportion of patients not requiring mechanical ventilation or ECMO	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04324021?cond=interferon+in+covid-19&draw=2&rank=7

Appendix 14. Calcineurin Inhibitors Studies for COVID 19: Cyclosporin A, Tacrolimus

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Banerjee D, et al	Case series (United Kingdom)	Tacrolimus + Azathioprine + CS; Azathioprine + CS; Tacrolimus + MMF	NA	COVID-19 who underwent renal transplant 45 – 69y/o (7)	Effect of immune-suppressive therapy on COVID 19 patients undergoing renal transplant	Suggest to suspend kidney transplant during the pandemic for high-risk recipients with comorbidities	Published	https://www.kidney-international.org/article/S0085-2538(20)30361-6/fulltext
Ning L, et al.	Case report (China)	Cyclosporin + LPV/r + CS	NA	COVID 19 who underwent renal transplant 29y/o (1)	Clinical presentation, severity & outcome of COVID 19 with solid organ transplant	Clinical recovery with no significant complications	Published	https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajt.15897
Bhoori S, et al.	Case series (Italy)	Cyclosporine; Tacrolimus	NA	COVID 19 post-liver transplant >65y/o (3)	Effects of immuno-suppressive therapy on post liver transplant recipients	All 3 patients died who rapidly developed ARDS	Published	https://www.thelancet.com/pdfs/journals/langas/PIIS2468-1253(20)30116-3.pdf
NCT04341038	Randomized, single, parallel assignment, (Spain)	Methylpred-nisolone + Tacrolimus	Standard care	COVID 19 with lung injury ≥18y/o (84)	Time to reach clinical stability	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04341038?term=Tacrolimus&cond=COVID-19&draw=2&rank=1

Appendix 15-A. Antiviral Agent Studies for COVID 19: Lopinavir/Ritonavir (LPV/r)

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Cao B, et al.	Randomized, open label, parallel assignment (China)	LPV/r	Standard Care	Severe COVID 19 >18y/o (199)	Time to clinical improvement & detectable viral RNA	No difference in the time to: - clinical improvement - detectable viral RNA	Completed	https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
Yuan, J, et al.	Retrospective descriptive (correlation) (China)	LPV/r + Ribavirin + IFN α	LPV/r + IFN α	Discharged COVID 19 7-39y/o (94)	Viral clearance & biochemical outcomes of discharge COVID 19	SARS COv-2 conversion time was correlated with length of hospital stay & decline in CK & LDH between 2 groups, suggesting benefit for treatment in COVID-19	Published	https://link.springer.com/article/10.1007%2Fs00011-020-01342-0
Li Y, et al.	Randomized, open label parallel assignment (China)	LPV/r; Arbidol	Standard care	Mild-moderate COVID 19 18-80 y/o (86)	At D7 & 14: -average time of (+) to (-) conversion of SARS-CoV-2 nucleic acid -improve-ment in symptoms & chest CT	No difference in: - (+) to (-) conversion rate - improve-ment in symptoms & chest CT; more patients on LPV/r progressed to severe/critical status	Pre-proof available	https://www.medrxiv.org/content/10.1101/2020.03.19.20038984v2.full.pdf+html

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04307693	Randomized, open label, Parallel assignment (South Korea)	LPV/r; HCQ	Standard care	Mild COVID 19 patients 16 – 99 y/o (150)	Viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=2&rank=1
NCT04330690	Randomized, open label, Parallel assignment (Canada)	LPV/r	Standard care	COVID 19 patients ≥ 6mo old (440)	Efficacy of intervention	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330690?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=2
NCT04286503	Randomized, open label, Parallel assignment (China)	Carrimycin	LPV/r, Arbidol, CQ	COVID 19 patients 18-75 y/o (520)	Time to no fever; resolution of pulmonary inflammation, (-) SARS-C0V 2 conversion rate	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04286503?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=4
NCT04321174	Randomized, single, Parallel assignment (Canada)	LPV/r	Standard care	High risk contact with COVID 19 ≥18 months (1,220)	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, 2 arm double blind, parallel assignment (Iran)	Levamisole + Budesonide/ Formoterol inhaler + LPV/r + HCQ	LPV/r + HCQ	COVID 19 patients with respiratory distreaa 15 – 100 y/o (30)	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, single, Parallel assignment (China)	LPV/r + Arbidol + Oseltamivir	Standard care	COVID 19 patients with pneumonia ≥18y/o (400)	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, open label, parallel assignment (China)	LPV/r + Xiyanping injection + IFN α nebulization	LPV/r + IFN α nebulization	COVID 19 patients ≥18y/o (80)	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, double blind, quadruple, parallel assignment (USA)	LPV/r; HCQ; Losartan	Placebo	COVID 19 patients ≥18y/o (4,000)	Difference in NIAID COVID-19 Ordinal Severity Scale scores	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04328012?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=9
NCT04261907	Randomized, open label, Parallel assignment (China)	ASC09/ ritonavir	LPV/r	COVID 19 patients with pneumonia 18 - 75y/o (160)	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
NCT04321993	Non-randomized, open label, parallel assignment (Canada)	LPV/r; HCQ; Baricitinib	Standard care	Moderate-severe COVID 19 patients ≥18y/o (1,000)	Clinical status of subject at day 15	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/record/NCT04321993?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=11

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04251871	Randomized, open label, parallel assignment (China)	Traditional Chinese Medicine (TMC) + LPV/r + IFN α neb	LPV/r + IFN α neb	COVID 19 14 – 80y/o (150)	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
NCT04315948	Randomize, open label, parallel assignment (France)	LPV/r; HCQ; Remdesivir; IFN-ß-1a	Standard care	COVID 19 patients ≥18y/o (3,100)	% 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, open label, Parallel assignment (China)	Xiyanping injection + LPV/r + IFN α neb	LPV/r + IFN α neb	COVID 19 patients 18 – 70 y/o (348)	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, open label, Parallel assignment (China)	Traditional Chinese Medicine + LPV/r + IFN α neb	LPV/r + IFN α neb	COVID 19 patients 14 – 80 y/o (150)	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, open label, Parallel assignment (Hongkong)	LPV/r + Ribavirin + IFN β	LPV/r	COVID 19 patients ≥18y/o (127)	Time to (-) naso-pharyngeal swab	NA	Completed	https://clinicaltrials.gov/ct2/show/record/NCT04276688?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=17
NCT04328480	Randomized, Open label, parallel assignment (USA)	Colchicine; LPV/r + Colchicine	Standard care + Colchicine	COVID 19 suspects with pneumonia ≥18y/o (2,500)	All-cause mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04328480?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=19
NCT04307693	Randomized, open label, parallel assignment (South Korea)	LPV/r	HCQ	Mild COVID 19 patients 16 – 99 y/o (150)	Viral load	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04307693?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=2&rank=1
NCT04330690	Randomized, open label, Parallel assignment (Canada)	LPV/r	Standard care	COVID 19 patients ≥ 6mo old (440)	Efficacy of intervention	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330690?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=2
NCT04328285	Randomized, double blind, triple, parallel assignment (France)	LPV/r; HCQ	Placebo	Healthcare worker exposed to suspect or confirmed COVID 19 ≥18y/o (1,200)	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

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04359095	Randomized, Open label, parallel assignment (Colombia)	LPV/r + HCQ + Azithromycin	HCQ; HCQ + LPV/r; HCQ + Azithromycin	Admitted COVID 19 > 18 y/o (1,600)	Mortality; severe adverse events related to treatment	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04359095?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=5
NCT04350684	Randomized triple, parallel assignment (Iran)	Arbidol + IFN-β 1a + LPV/r + HCQ	IFN-B1a + LPV/r + HCQ	COVID 19 >18y/o (40)	Time to clinical improvement	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04350684?term=Arbidol&cond=COVID+19&draw=2&rank=1
NCT04364022	Randomized open label, parallel assignment (Geneva)	LPV/r + HCQ	None	Close contact of confirmed COVID 19 >18y/o (420)	21-day incidence of COVID-19 in individuals exposed to COVID 19 with no symptoms	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04364022?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=12
NCT04350671	Randomized triple, parallel assignment (Iran)	IFN-B1a + LPV/r + HCQ	LPV/r + HCQ	Admitted COVID 19 > 50 y/o (40)	Time to clinical improvement	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04350671?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=13
NCT04351724	Randomized, open label, parallel assignment (Austria)	HCQ + LPV/r; Rivaroxaban; RAS blocker; Clazakizu-mab	Standard care; thrombopro-phylaxis; non-RAS blocker; placebo	Admitted COVID 19 > 18 y/o (500)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04351724?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=17
NCT04365582	Randomized, open label, parallel assignment (France)	Azithromycin + HCQ + LPV/r	Standard care	COVID 19 > 50 y/o (640)	Hospital admission	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04365582?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04343768	Randomize, open label, parallel assignment (Iran)	HCQ + LPV/r + IFN-B1a or IFN-B1b	HCQ + LPV/r	COVID 19 > 18 y/o (60)	Time to clinical improvement	NA	Completed	https://clinicaltrials.gov/ct2/show/record/NCT04343768?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=20
NCT04366245	Randomized, open label, parallel assignment (Spain)	Hyper-immune plasma	Azithromycin + HCQ + LPV/r + IFN-B1b	COVID 19 > 18 y/o (72)	Safety Efficacy	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04366245?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=21
NCT04320277	Randomized, Open label, crossover assignment (Italy)	Baricitinib + LPR/r	LPV/r ± HCQ	Mild to moderate COVID 19 18-85 y/o (60)	% of patients requiring transfer to ICU	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04320277?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=23
NCT04275388	Randomized, open label, parallel assignment (China)	Xiyanping injection + LPV/r + IFN a neb	LPV/r + IFN a neb	Mild to moderate COVID 19 18-10 y/o (348)	Clinical recovery time	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04275388?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=24
NCT04361422	Randomized, Open label, parallel (Egypt)	Isotretinoin + LPV/r	HCQ + LPV/r + Oseltamivir + Azithromy-cin or Clari-thromycin + Vit C + Cyanoco-balamine	COVID -19 18-40y/o (300)	Clinical clearance (14-30 days)	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04361422?term=oseltamivir&cond=covid+19&draw=1&rank=10
NCT04323345	Randomized, single, parallel Assignment (Egypt)	Natural honey;	LPV/r or Arbidol or HCQ or Oseltamivir ± azithro-mycin	COVID 19 5 - 75y/o (1,000)	Rate of (-) swabs; no fever; resolution of lung inflammation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04323345?term=oseltamivir&cond=covid+19&draw=1&rank=6

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT02735707	Randomized, open label, factorial assignment (REMAP-CAP)	Oseltamivir; LPV/r; HCQ + LPV/r; Ritonavir; IFN-B1a; Anakinra; CS; Tocilizumab; Sarilumab	Standard care; no anti-viral agent	Severe to critical suspected or confirmed COVID -19 >18y/o (7,100)	All-cause mortality (90 days); days alive & outside of ICU (21 days)	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT02735707?term=oseltamivir&cond=covid+19&draw=1&rank=8
NCT04368351	Observational, case control (Italy)	Probiotics + Azithromycin + HCQ	Azithromycin + LPV/r or Ritonavir + HCQ	Admitted COVID 19 >18y/o (70)	Resolution of acute diarrhea	NA	Active not recruiting	https://clinicaltrials.gov/ct2/show/NCT04368351?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=31
NCT04359667	Observation-al, prospective (Croatia)	Tocilizumab	Tocilizumab + HCQ + LPV/r + Remdesivir	Severe COVID 19 >18y/o (30)	role of laboratory markers as predictors of survival in severe COVID-19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04359667?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=32
NCT04366089	Randomized, single, parallel assignment (Italy)	Oxygen–Ozone + Probiotics	Azithromycin + LPV/r + Ritonavir + HCQ + Darunavir	Admitted COVID 19 >18y/o (152)	# of patients requiring orotracheal intubation despite treatment	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04366089?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=2&rank=34
NCT04353180	Randomized, open label, parallel (Egypt)	Isotretinoin + HCQ + LPV/r + Oseltamivir + Azithromy-cin or Clari-thromycin + Vit C + Cyanoco-balamine	Standard care	Severe to critical COVID-19 18-80y/o (45)	Proportion of lung injury score after treatment	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04353180?term=oseltamivir&cond=covid+19&draw=1&rank=12

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04303299	Randomized, open label, parallel assignment (Thailand)	Various combinations of: -Oseltamivir, -Favipiravir, -HCQ -LPV/r	Conventional quarantine	COVID 19 16-100y/o (320)	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
NCT04278404	Observation-al, prospective (Canada, US)	LPV/r or other prescribed drugs of interest (DOI) of routine medical care	NA	COVID 19 & patients with co-morbidities < 21 y/o (5,000)	Pharmaco-kinetics of DOIs	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04278404?term=Ribavirin&cond=COVID+19&draw=1&rank=6
EudraCT 2020-001113-21	Randomized, open label parallel assignment (United Kingdom)	LPV/r; CS; HCQ; Azithromycin; Tocilizumab	Standard care	Admitted COVID 19 admitted <18y/o (1,000)	All-cause mortality	NA	Ongoing	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001113-21/GB
ACTRN12620000445976	Randomized open label parallel assignment (Australia)	LPV/r; HCQ; LPV/r + HCQ	Standard care	Mild COVID 19 ≥18y/o (2,500)	Proportion of participants alive and not requiring intensive respiratory support	NA	Not yet recruiting	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379542&isReview=true
NCT04360980	Randomized, double blind, parallel assignment (Iran)	LPV/r + Azithromycin + Ceftriaxone + Vitamins	Colchicine	COVID 19 >18y/o (80)	Increasing inflammatory status; Clinical deterioration; PCR Viral Load; Change in chest CT	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04360980?term=Lopinavir+%2F+Ritonavir&cond=COVID+19&draw=1&rank=38

Appendix 15-B. Antiviral Agent Studies for COVID 19: Ribavirin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Yuan, J, et al.	Retrospective descriptive (correlation) (China)	LPV/r + Ribavirin + IFN α	LPV/r + IFN α	Discharged COVID 19 7-39y/o (94)	Viral clearance & biochemical outcomes of discharge COVID 19	SARS COv-2 conversion time was correlated with length of hospital stay & decline in CK & LDH between 2 groups, suggesting benefit for treatment	Published	https://link.springer.com/article/10.1007%2Fs00011-020-01342-0
Hung IFN, et al.	Randomized, open-label, Parallel assignment (Hongkong)	LPV/r + Ribavirin + IFN β-1B	LPV/r	Hospitalized Patients with COVID 19 ≥18 y/o (127)	Time to negative NPS for SARS-Cov-2 viral RT-PCR	LPV/r + Ribavirin + IFN β1B were safe & superior to LPV/r in shortening virus shedding, alleviating symptoms & facilitating discharge of patients with mild to moderate COVID 19.	Published	https://clinicaltrials.gov/ct2/show/NCT04276688?cond=interferon+in+covid-19&draw=2&rank=11
NCT04276688	Randomized, open label, Parallel assignment (Hongkong)	LPV/r + Ribavirin + IFN β	LPV/r	COVID 19 patients ≥18 y/o (127)	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

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04356677	Non randomized, open label, parallel assignment (US)	Ribavirin	Standard care	COVID 19 ≥18y/o (50)	Change in clinical status severity rating	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04356677?term=ribavirin&cond=covid+19&draw=1&rank=1
NCT04278404	Observation-al, prospective (Canada, US)	Ribavirin or other prescribed drugs of interest (DOI) of routine medical care	NA	COVID 19 & patients with co-morbidities < 21 y/o (5,000)	Pharmaco-kinetics of DOIs	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04278404?term=Ribavirin&cond=COVID+19&draw=1&rank=6

Appendix 15-C. Antiviral Agent Studies for COVID: Umifenovir (Arbidol)

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Li L, et al.	Retrospective cohort (China)	Arbidol	LPV/r + IFN	COVID 19 >18y/o (111)	Viral clearance, radiologic improvement; O2 therapy requirement	Arbidol could enhance viral clearance, chest CT improvement & reduce demand for O2 therapy	Published	https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3542148
Zhang J, et al.	Retrospective case control (China)	Arbidol	Oseltamivir	Family members (66) or health care workers with no standard respiratory protection (124) exposed to COVID-19	Occurrence of fever or respiratory symptoms within 24 days of exposure & confirmed by RT-PCR	Arbidol could reduce the infection risk	Published	http://www.chinaxiv.org/abs/202002.00065

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Zhu Z, et al.	Retrospective (China)	Arbidol	LPV/r	COVID 19 >18y/o (50)	Detection of viral load on day 7 and day 14	No difference in fever duration; arbidol group had shorter duration of (+) RNA test compared to LPV/r	Published	https://doi.org/10.1016/j.jinf.2020.03.060
NCT04286503	Randomized, open label, parallel assignment (China)	Carrimycin	Arbidol; LPV/r; CQ	COVID 19 patients with pneumonia 18-75 y/o (520)	Time to no fever & pulmonary inflammation resolution; (-) conversion of SARS-CoV 2	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04286503?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=4
NCT04260594	Randomized, open label, parallel assignment (China)	Arbidol	Standard care	COVID 19 patients with pneumonia 18 – 75 y/o (380)	Virus (-) 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 (China)	Arbidol + IFN α2b + Bromhexine	Arbidol + IFN α2b	Patients suspected or confirmed w/ COVID 19 pneumonia 18 -80y/o (60)	Time to clinical recovery after treatment, rate of aggravation	NA	Active not recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04273763?term=Arbidol&cond=Covid+19&draw=2&rank=3
NCT04323345	Randomized, Single. Parallel assignment (Egypt)	Natural honey	Arbidol; LPV/r; HCQ; CQ; Oseltamivir ± Azithromycin	COVID 19 patients 5 – 75 y/o (1,000)	Recovery rate to (-) swabs; normal temperature; resolution of radiologic lung inflammation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04323345?term=Lopinavir+%2F+Ritonavir&cond=COVID-19&draw=1&rank=13

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04350684	Randomized, triple, parallel assignment (Iran)	Arbidol + IFN-β 1a + LPV/r + HCQ	IFN-B1a + LPV/r + HCQ	COVID 19 patients >18y/o (40)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04350684?term=Arbidol&cond=COVID+19&draw=2&rank=1
NCT04261907	Randomized, Open label, parallel assignment (China)	ASC09/ ritonavir	LPV/r	COVID 19 patients with pneumonia with onset of symptoms ≤ 7 days 18 - 75y/o (160)	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 15-D. Antiviral Agent Studies for COVID 19: Remdesivir

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Grein J, et al.	Cohort study (US, Japan, Europe, Canada)	Remdesivir	NA	Severe COVID 19 23 – 52y/o (53)	Clinical improvement	Clinical improvement was observed in 36 of 53 patients (68%).	Published	https://www.nejm.org/doi/full/10.1056/NEJMoa2007016
Wang Y, et al.	Randomized, quadruple double blind, parallel assignment (China)	Remdesivir	Placebo	COVID 19 patients ≥18 y/o (237)	Time to clinical improvement	No significant benefits for remdesivir over standard care	Published	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04280705 (NIH)	Randomized, double blind, parallel assignment (USA)	Remdesivir	Placebo	COVID 19 patients 18 – 99 y/o (1,063)	% of subjects reporting each severity rating	31% had faster time to recovery than placebo; median time to recovery (11 days) than placebo (15 days); mortality rate (8.0%) than placebo (11.6%)	Preliminary report	https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19
NCT04365725	Observation-al retrospective (France)	Remdesivir	NA	COVID-19 Adult (200)	Clinical course on D15	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/NCT04365725?term=Remdesivir&cond=COVID+19&draw=2&rank=1
NCT04292899	Randomized, open label, Parallel assignment (USA)	Remdesivir	Standard care	COVID 19 patients ≥ 12y/o (6,000)	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, open label, Parallel assignment (USA)	Remdesivir	Standard care	Moderate COVID 19 patients ≥12 y/o (1,600)	Proportion of participants discharged by D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/results/NCT04292730?term=Remdesivir&cond=COVID+19&draw=2&rank=2
NCT04252664	Randomized, quadruple double blind, parallel assignment (China)	Remdesivir	Placebo	COVID 19 patients with pneumonia ≥18 y/o (308)	Time to clinical recovery	NA	Suspended	https://clinicaltrials.gov/ct2/show/record/NCT04252664?term=Remdesivir&cond=COVID+19&draw=2&rank=3

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04321616	Randomized, open label, Parallel assignment (Norway)	Remdesivir + HCQ	Standard care	COVID 19 patients ≥18 y/o (700)	In-hospital mortality	NA	Not yet Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04321616?term=Remdesivir&cond=COVID+19&draw=2&rank=6
NCT04315948	Randomized, open label, parallel assignment (France)	Remdesivir + LPV/r + IFN-ß-1a + HCQ	Standard care	COVID 19 patients with respiratory distress ≥18 y/o (3,100)	% 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
NCT04323761	Randomized, open label, parallel assignment (USA)	Remdesivir	Standard care	COVID 19 patients ≥12y/o	Odds ratio for improvement on a 7-point Ordinal Scale on D14	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04323761?term=Remdesivir&cond=COVID+19&draw=2&rank=6
EduraCT 2020-000982-18	Randomized, open label, parallel assignment (Norway)	Remdesivir	Standard care	COVID 19 admitted in ICU ≥18y/o (443)	All-cause in-hospital mortality.	NA	Ongoing	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-000982-18/NO#E
NCT04330690	Randomized, open-label, parallel assignment (Canada)	Remdesivir	HCQ; LPV/r	Admitted COVID-19 Adult (440)	Efficacy of Interventions	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330690?term=Remdesivir&cond=COVID+19&draw=2&rank=7
NCT04302766	Randomized, open label, parallel assignment (USA)	Remdesivir	Standard care	COVID-19 All ages (440)	Odds ratio for improvement on a 7-point Ordinal Scale on D14	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04302766?term=Remdesivir&cond=COVID+19&draw=2&rank=10

Appendix 15-E. Antiviral Agent Studies for COVID 19: Favipiravir

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Chen C, et al.	Randomized, open label parallel assignment (China)	Favipiravir	Arbidol	COVID 19 18 – 99y/o (239)	Clinical recovery rate	Favipiravir did not significantly improve the clinically recovery rate at Day 7 compared to Arbidol.	Published	https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4.full.pdf
Cai Q, et al.	Non randomized Open label (China)	Favipiravir	LPV/r	COVID 19 16-75y/o (59)	Viral clearance; radiologic improvement	Favipiravir group appeared to have faster viral clearance & better chest imaging change compared to LPV/r.	Published	https://doi.org/10.1016/j.eng.2020.03.007
NCT04333589	Randomized open label, parallel assignment (China)	Favipiravir	Standard care	COVID 19 18 – 80 y/o (210)	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, double blind, Parallel assignment (Italy)	Favipiravir	Placebo	COVID 19 18 – 75 y/o (100)	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
NCT04303299	Randomized, open label, parallel assignment (Thailand)	Various combinations of: -Oseltamivir, -Favipiravir, -HCQ -protease inhibitors	Conventional quarantine	COVID 19 16-100 y/o (320)	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

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04310228	Randomized, open label, parallel assignment (China)	Favipiravir + Tocilizumab	Faviripavir; Tocilizumab	COVID 19 with elevated IL 6 18-65 y/o (150)	Clinical cure rate	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04310228?term=Favipiravir&cond=COVID+19&draw=2&rank=3
NCT04333589	Randomized, open label, parallel assignment (China)	Favipiravir	Standard care	COVID 19 18 – 80 y/o (210)	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
NCT04359615	Randomized double blind, parallel assignment (Iran)	Favipiravir	HCQ	COVID 19 ≥18y/o (40)	Time to clinical improvement	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04359615?term=Favipiravir&cond=COVID+19&draw=3&rank=2
NCT04358549	Randomized, open label, parallel assignment (US)	Favipiravir	Standard Care	COVID 19 18 – 80 y/o (50)	Time to viral clearance	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04358549?term=Favipiravir&cond=COVID+19&draw=3&rank=3
NCT04349241	Randomized, open label, parallel assignment (Egypt)	Favipiravir	Standard Care	COVID 19 18 – 80 y/o (100)	Viral clearance & clinical improvement	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04349241?term=Favipiravir&cond=COVID+19&draw=3&rank=4
NCT04346628	Randomized, open label, parallel assignment (US)	Favipiravir	Standard Care	COVID 19 ≥18y/o (120)	Time until cessation of oral shedding of SARS-CoV-2 virus	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04346628?term=Favipiravir&cond=COVID+19&draw=3&rank=8

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04351295	Randomized, open label, parallel assignment (Egypt)	Favipiravir	Placebo	COVID 19 Child, adult, older adult (40)	# of patients with viral cure	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04351295?term=Favipiravir&cond=COVID+19&draw=3&rank=9
NCT04356495	Randomized open-label, parallel assignment (France)	HCQ; Imatinib; Favipiravir; Telmisartan	Vitamins	COVID 19 ≥65y/o (50)	Proportion of patients hospitalized; death	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04356495?term=Favipiravir&cond=COVID+19&draw=3&rank=10
NCT04345419	Randomized, single parallel assignment (Egypt)	CQ; Favipiravir; Nitazoxanide; Ivermectine; Niclosamide; Oseltamivir	NA	COVID 19 child, adult, older adult (120)	# of patients with decreased viral load	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04345419?term=Favipiravir&cond=COVID+19&draw=3&rank=12

Appendix 15-F. Antiviral Agent Studies for COVID 19: Oseltamivir

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04303299	Randomized, open label, parallel assignment (Thailand)	Oseltamivir + HCQ; Darunavir + Ritonavir + Oseltamivir + HCQ; LPV/r+ Oseltamivir	Conventional Quarantine	COVID 19 >16 y/o (320)	Eradication of NPS SARS-CoV-2	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04303299?term=oseltamivir&cond=covid+19&draw=2&rank=1
NCT04261270	Randomized Single, parallel assignment (China)	ASC09F + Oseltamivir; Ritonavir + Oseltamivir; Oseltamivir	NA	COVID 19 18 – 55y/o (60)	Rate of adverse outcome: -SPO2 <93% without O2 -PaO2/FiO2 <300mmHg -RR >30bpm without O2 therapy	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04261270?term=oseltamivir&cond=covid+19&draw=2&rank=4

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04338698	Randomized double blind, parallel assignment (Pakistan)	HCQ; Azithromycin; Oseltamivir; various combinations of the 3 drugs	Standard care	COVID 19 >18 y/o (500)	(-) conversion on RT-PCR or viral load < 150 i.u; clinical improvement	N/A	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04338698?term=oseltamivir&cond=covid+19&draw=2&rank=2
NCT04255017	Randomized single, parallel Assignment (China)	Arbidol; Oseltamivir; LPV/r	NA	COVID 19 >18 y/o (400)	Rate of disease remission (in 2 weeks); time for lung recovery by imaging (in 2 weeks)	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04255017?term=oseltamivir&cond=covid+19&draw=2&rank=3
NCT04349241	Randomized, open label, parallel assignment (Egypt)	Favipiravir	Oseltamivir	Mild-moderate COVID 19 18 – 80y/o (100)	2 successive (-) COVID-19 PCR analysis tests 48-72 hours apart; normal body temperature for 48 hours	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04349241?term=oseltamivir&cond=covid+19&draw=1&rank=5
NCT04323345	Randomized, single, parallel assignment (Egypt)	Natural honey + standard care	LPV/r or Arbidol or HCQ or Oseltamivir ± Azithromycin	COVID 19 5 - 75y/o (1,000)	(+) to (-) NPS & normal temperature; resolution of lung inflammation	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04323345?term=oseltamivir&cond=covid+19&draw=1&rank=6
NCT04348877	Open label, single group assignment (Egypt)	CP	Oseltamivir + HCQ ± Azithromycin	Severe or life threatening COVID 19 18- 80y/o (1,000)	2 successive (-) RT-PCR analysis tests 72 hours apart	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04348877?term=oseltamivir&cond=covid+19&draw=1&rank=7

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT02735707	Randomized, open label, factorial Assignment (REMAP-CAP)	No antivirals	Oseltamivir; LPV/r; HCQ; HCQ + LPV/r; IFN-B1a; Anakinra; CS; Tocilizumab; Sarilumab	Severe - critical suspected or confirmed COVID -19 >18y/o (7,100)	All-cause mortality; days alive & outside of ICU	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT02735707?term=oseltamivir&cond=covid+19&draw=1&rank=8
NCT04361422	Randomized, Open label, parallel assignment (Egypt)	Isotretinoin	HCQ + Oseltamivir + Azithromycin + Vit C + Cyanocobalamine + LPV/r	COVID -19 18-40y/o (300)	Clinical clearance	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04361422?term=oseltamivir&cond=covid+19&draw=1&rank=10
NCT04353180	Randomize, open label, parallel assignment (Egypt)	Isotretinoin	HCQ + Oseltamivir + Azithromycin or Clarithromycin + Vit C + Cyanocobalamin + LPV/r	Severe - critical COVID-19 18-80y/o (45)	Proportion of lung injury score - decreased or increased after treatment	NA	Recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04353180?term=oseltamivir&cond=covid+19&draw=1&rank=12
NCT04345419	Randomized, single, parallel assignment (Egypt)	Chloroquine; Favipavir; Nitazoxanide; Ivermectin; Niclosamide; Oseltamivir	NA	COVID- 19 All ages (120)	# of patients with decreased viral load (6 months)	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/record/NCT04345419?term=oseltamivir&cond=covid+19&draw=1&rank=13&view=record

Appendix 16. Aspirin Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04363840	Randomized, Open label Parallel assignment (USA)	Aspirin + Vitamin D	Standard care	COVID 19 with low Vit D & DIC ≥18y/o (1,080)	Reduction in hospitalize-tion rates for COVID 19 patients	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04363840?term=Aspirin&cond=COVID&draw=2&rank=1
NCT04343001	Randomized, open-label, factorial, randomized (UK)	Aspirin; Losartan; Simvastatin; In various combinations	Standard care	COVID 19 patients ≥40y/o (10,000)	Cause of death	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04343001?term=Aspirin&cond=COVID&draw=2&rank=2
NCT04365309	Randomized, Open label, parallel assignment (China)	Aspirin	Standard care	COVID 19 with pneumonia 18 - 85 y/o (128)	Clinical recovery time	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04365309?term=Aspirin&cond=COVID&draw=2&rank=3
NCT04368377	Non-randomized, Open label, single group assignment (Italy)	Aspirin + Tirofiban + Clopidogrel + fondaparinux	NA	COVID19 with pneumonia & DIC ≥18y/o (5)	P/F ratio, PaO2 & A-a O2 differences	N/A	completed	https://clinicaltrials.gov/ct2/show/NCT04368377?term=Aspirin&cond=COVID&draw=2&rank=4
NCT04333407	Randomized, open label, parallel assignment (UK)	Aspirin + Clopidogrel + Rivaroxaban + Atovastatin + Omepra-zole	Standard care	COVID 19 Admitted with DM or coronary disease or hypertension 18 – 85y/o (3,170)	All-cause mortality	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04333407?term=Aspirin&cond=COVID&draw=2&rank=5

Appendix 17. Colchicine Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04355143	Randomized, open label, parallel assignment (USA)	Colchicine	Standard care	COVID-19 patients with cardiac injury ≥18y/o (150)	Maximum troponin level	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04355143?cond=colchicine%2C+covid&draw=2&rank=1
NCT04360980	Randomized, double blind, parallel assignment (Iran)	Colchicine	Standard care	COVID-19 patients ≥18y/o (80)	Clinical deterioration; viral Load change; CT severity involvement index	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04360980?cond=colchicine%2C+covid&draw=2&rank=2
NCT04350320	Randomized, open-label, Parallel assignment (Spain)	Colchicine	Standard care	COVID-19 patients ≥18y/o (102)	Changes in patients' clinical status with 7 points ordinal scale WHO; change in IL-6 values	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04350320?cond=colchicine%2C+covid&draw=2&rank=3
NCT04326790	Randomized, open labeled, Parallel assignment (Greece)	Colchicine	Standard care	COVID-19 patients ≥18y/o (180)	CRP increase 3x normal limit; clinical deterioration; maximal concentration of cardiac troponin	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04326790?cond=colchicine%2C+covid&draw=2&rank=4
NCT04322565	Randomized, open label, parallel assignment (Italy)	Colchicine	Standard care	COVID-19 patients with pneumonia 18 – 100y/o (310)	Clinical improvement; hospital discharge	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04322565?cond=colchicine%2C+covid&draw=2&rank=5

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04322682	Randomized, double-blind, parallel assignment (Canada)	Colchicine	Placebo	COVID-19 infection within last 24 hours Outpatient (6,000)	Number of patients who die or need to be admitted	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04322682?cond=colchicine%2C+covid&draw=2&rank=6
NCT04363437	Randomized, open label, parallel assignment (USA)	Colchicine	Standard care	COVID-19 patients 18 – 120y/o (70)	% of patients requiring escalation of supplemental oxygen beyond low-flow nasal cannula	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04363437?cond=colchicine%2C+covid&draw=2&rank=7
NCT04367168	Randomized, double blind, parallel assignment (Mexico)	Colchicine	Placebo	COVID-19 patients >18 y/o (174)	Improvement in symptoms & blood test results; progression to severe disease	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04367168?cond=colchicine%2C+covid&draw=2&rank=5
NCT04328480	Randomized, open label, parallel assignment (Argentina)	Colchicine	Standard care	COVID-19 patients >18 y/o (2,500)	All-cause mortality	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04328480?cond=colchicine%2C+covid&draw=2&rank=9
NCT04363437	Randomized, open labeled, Parallel assignment (USA)	Colchicine	Standard care	Moderate-severe COVID-19 patients >18 y/o (70)	% of Patients requiring supplemental oxygen beyond 8L nasal cannula	NA	Recruiting	https://clinicaltrials.gov/ct2/show/study/NCT04363437?cond=colchicine+covid&draw=1&rank=7

Appendix 18. Angiotensin Converting Enzyme Inhibitor (ACEi) and Angiotensin Receptor Blocker (ARB) Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04330300	Randomized, open label, parallel assignment (Ireland)	Thiazide + Ca channel blocker	ACEi/Angiotensis Receptor Blocker (ARB)	COVID 19 on ACEi/ARB ≥60y/o (2,414)	Covid patients who die	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04330300
NCT04353596	Randomized, Open label, parallel assignment (Germany)	Discontinued maintenance ACEi/ARB	ACEi/ARB	COVID 19 on ACEi/ARB ≥18y/o (208)	Sequential organ failure assessment score & death; admission to ICU	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04353596
NCT04318418	Observation-al, retrospective (Italy)	Patients developed severe COVID 19	Patients did not develop severe COVID-19	COVID 19 on ACEi/ARB All ages (5,000)	Severe COVID 19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04318418
NCT04338009	Randomized, Single, parallel assignment (USA)	Discontinued ACEi/ARB; continued ACEi/ARB	NA	Suspected COVID 19 on ACEi/ARB ≥18y/o (152)	Hierarchical component endpoint	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04338009
NCT04331574	Observation-al, cross sectional (Italy)	ACEi/ARB maintenance	NA	COVID 19 on ACEi/ARB 18-120y/o (2,000)	Chronic intake modifies prevalence & severity of COVID-19	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04331574
NCT04329195	Randomized, open label, parallel assignment (France)	Discontinued ACEi	Continued ACEi	COVID 19 on ACEi/ARB ≥18y/o (554)	Time to clinical improvement	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04329195
NCT04356417	Observational, cohort (France)	Continued ACEi/ARB	Antimalarial drug	COVID 19 on ACEi/ARB ≥18y/o (6,000,000)	Severe COVID-19	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04356417?

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04357535	Observatoin-al, cohort (Saudi Arabia)	Continued ACEi/ARB	NA	COVID-19 on ACEi/ARB ≥18y/o (226)	Rate of requirement for mechanical ventilation	NA	Terminated	https://clinicaltrials.gov/ct2/show/NCT04357535
NCt04328012	Randomized, double blind, quadruple (USA)	LPV/r; HCQ; Losartan	Placebo	COVID 19 ≥18y/o (4,000)	COVID-19 Ordinal Severity Scale (NCOSS)	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04328012
NCT04312009	Randomized, Quadruple, parallel assignment (USA)	Losartan	Placebo	COVID-19 With ARDS ≥18y/o (200)	Difference in estimated P/F ratio at D7	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04312009
NCT4311177	Randomized, quadruple, parallel assignment (USA)	Losartan	Placebo	COVID 19 With ARDS ≥18y/o (580)	Hospital admission	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04311177
NCT04322786	Observation-al, prospective (England)	Continued ACEi	Control without ACEi	Cases on ACEi & normal subjects ≥18y/o (1,302,508)	Incidence of COVID 19	NA	Active, not recruiting	https://clinicaltrials.gov/ct2/show/NCT04322786

Appendix 19. Statin Studies for COVID 19: Atorvastatin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
IRCT20190727044343N2	Randomized, 2-arm blinded, parallel assignment (Iran)	Atorvastatin	Standard care	COVID-19 patients w/o prior cardio-vascular dse 20 – 50y/o (100)	Mortality; hospital discharge; CRP level; duration of hospital stay	N/A	Recruitment complete	http://en.irct.ir/trial/46639

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04333407	Randomized, open label, parallel assignment (England)	Atorvastatin + Clopido-grel + Rivar-oxaban + Atorvastatin + Ome-prazole	Standard care	COVID-19 patients 18 – 85y/o (3,170)	All-cause mortality at D30	N/A	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04333407

Appendix 20. Alpha-1 (α1) Adrenergic Receptor Antagonist Study for COVID: Prazosin

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
Konig MF, et al.	Retrospective analysis of 2 cohorts	α1-AR antagonists	Without α1-AR antagonists	COVID 19 adults on α1-AR antagonists 1st cohort (13,125); 2nd cohort (108,956)	role for α1-AR antagonists in preventing poor outcomes resulting from pulmonary hyper-inflammatory responses	Support a clinical rationale for studying α1-AR antagonists in the prophylaxis of severe COVID-19 & states of local & systemic immune dysregulation	Published	https://www.medrxiv.org/content/10.1101/2020.04.02.20051565v2.full.pdf
NCT04365257	Randomized. open label, parallel assignment (USA)	Prazosin	Standard care	COVID 19 45 – 85y/o (220)	Death; requiring O2 support or mechanical ventilation; adverse events; symptomatic hypotension	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04365257?cond=alpha+1+antagonist+for+COVID+19&draw=2&rank=1

Appendix 21. 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 (Brazil)	MSCs	None	Severe COVID 19 Pneumonia ≥18y/o (66)	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
NCT04313322	Open label, single group assignment (Saudi Arabia)	WJ-MSCs	NA	Patients with COVID 19 ≥18y/o (5)	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, double-blind, quadruple, parallel assignment (China)	MSCs	Placebo	COVID 19 patients with severe convalesc-ence 18 - 75y/o (90)	Size of lesion area; severity of pulmonary fibrosis; 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, parallel assignment (China)	Allogeneic human dental pulp stem cells	Placebo	Severe COVID 19 Pneumonia 18 – 65y/o (20)	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 (China)	UC-MSCs	Placebo	Severe COVID 19 disease 18 – 65y/o (48)	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, partial assignment (China)	UC-MSCs	Placebo	COVID 19 Pneumonia 18 – 75y/o (30)	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 (USA)	Dental pulp mesenchy-mal stem cells	NA	Severe COVID 19 pneumonia 18 – 75y/o (24)	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 (China)	MSCs	None	COVID 19 Pneumonia 18 – 70y/o (20)	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 (USA)	MSCs.	NA	COVID 19 induced acute respiratory failure ≥18y/o (30)	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 (China)	UC-MSCs	NA	Serious and critical COVID Pneumonia 18 -75y/o (10)	Oxygenation index	NA	recruiting	https://clinicaltrials.gov/ct2/show/NCT04269525?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=11
NCT04333368	Randomized, triple, parallel assignment (France)	Umbilical cord Wharton's jelly-derived human MSC	Placebo	COVID 19 related ARDS ≥18y/o (60)	Respiratory efficacy evaluated by increase in PaO2/FiO2 ratio baseline to D7	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04333368?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=12
NCT04341610	Randomized, double-blind, quadruple, parallel assignment (Denmark)	Allogeneic adipose-derived mesenchy-mal stromal cells	Placebo	Severe COVID 19 respiratory disease 18 - 80y/o (40)	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 (China)	MSCs-derived exosomes	NA	Patients with severe COVID 19 Pneumonia 18 – 75y/o (30)	Adverse reaction	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04276987?term=mesenchymal+stem+cells&cond=COVID&draw=3&rank=15

Appendix 22. BGC Vaccine Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04328441	Randomized, quadruple, parallel assignment (Netherland)	BCG vaccine	Placebo (0.9% saline)	Health care workers exposed to COVID 19 ≥18y/o (1,500)	Health care workers absenteeism	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04328441

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04327206	Randomized, double blinded, parallel assignment (Australia)	BCG vaccine	Placebo (0.9% saline)	Health care workers exposed to COVID 19 ≥18y/o (10,078)	COVID-19 disease incidence among the health care workers	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04327206

Appendix 23. Vitamin C Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04323514	Open label, single group assignment (Italy)	Vit C	NA	COVID 19 with pneumonia (500)	Change of mortality	NA	Recruiting	https://www.clinicaltrials.gov/ct2/show/NCT04323514
NCT04264533	Randomized, triple, parallel assignment (China)	Vit C	Placebo (Sterile H2O)	Critical COVID 19 ≥18 y/o (140)	Ventilation free days	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04264533
NCT03680274	Randomized, quadruple, parallel assignment (Canada)	Vit C	Placebo (D5W)	COVID 19 in ICU ≥18 y/o (800)	Deceased participants or persistent organ dysfunction	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT03680274
NCT04363216	Randomized, Open label, sequential assignment (USA)	Vit C	Standard Care	Covid-19 ≥18y/o (66)	Clinical improvement	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04363216
NCT04344184	Randomized, Quadruple, parallel assignment (USA)	Vit C	Placebo (D5W)	COVID-19 with acute lung injury ≥18y/o (200)	# of ventilator free days	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04344184

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04342728	Randomized, Open label, single group assignment (USA)	Vit C; zinc gluconate; Vit C + zinc gluconate	Standard care	COVID 19 ≥18y/o (520)	Symptom reduction	NA	Enrolling by invitation	https://clinicaltrials.gov/ct2/show/NCT04342728
NCT04357782	Non-randomized; open label, single group assignment2 (USA)	Vit C	Mild or severe Deoxygena-tion	COVID 19 with hypoxia ≥18y/o (20)	Incidence of adverse events	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04357782

Appendix 24. Vitamin D Studies for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04334005	Randomized, double blind, parallel assignment (Spain)	Standard care	Vitamin D	COVID 19 patients 40 - 70y/o (200)	Cumulative death for all causes	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04334005
NCT04344041	Randomized, open label, parallel assignment (France)	Vitamin D (high dose)	Vitamin D (standard dose)	COVID 19 patients ≥70y/o (260)	Number of deaths of any cause	NA	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04344041
ChiCTR2000029732	Observational, factorial (China)	Vitamin D Deficiency group	NA	COVID 19 patients with pneumonia ≥18y/o (104)	ROX index	NA	Recruiting pending	http://www.chictr.org.cn/hvshowproject.aspx?id=22257

Appendix 25. Zinc Study for COVID 19

Author/ Study Identifier	Study design	Intervention	Comparator	Population	Primary outcome	Results	Status	Source (hyperlink)
NCT04351490	Randomized, Open label, parallel assignment (USA)	Zinc + 25-OH cholecalcife-rol	Standard care	COVID 19 ≥60y/o (3,140)	Survival rate in asymptom-atic subjects	NA	Not yet recruiting	https://clinicaltrials.gov/ct2/show/NCT04351490?

Appendix 26. Availability of the immunomodulators in the Philippines

FDA approved	**NOT available**
ACE inhibitor Adalimumab Anaferon Aspirin Azathioprine BCG Colchicine Convalescent plasma Corticosteroid (Methylprednisolone, prednisolone, prednisone, hydrocortisone, dexamethasone) Cyclosporin A DHA/Omega 3 fatty acids Inosine pranobex Interferon α, β, γ, α 2a, α 2b, β 1a, β 1b IVIG Lopinavir/ritonavir Melatonin Mesenchymal stem cell Prazocin Probiotics Quercetin Remdesivir Ribavirin Statins Tocilizumab Vitamin C, Vitamin D Zinc sulfate	Adalimumab Aldesleukin Alpha reactive antibodies Anakinra Arbidol Baricitinib Canakimumab Emapalumab Favipiravir Hyperimmune Immunoglobulin Lenzimumab Leronlimab Ruxolitinib Sarilumab Siltuximab Oseltamivir

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