Philippine Society of Allergy, Asthma and Immunology, Inc.

A REVIEW OF IMMUNOMODULATORS AS THERAPEUTIC INTERVENTIONS FOR MODERATE TO SEVERE COVID-19 INFECTIONS (Version 4.2, August 15, 2021)

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Contributors:

Fellows and Diplomates of the Philippine Society of Allergy, Asthma and Immunology, Inc.

Jovilia M. Abong, MD
Maria Socorro Agcaoili-De Jesus, MD
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Cynthia Purificacion Ybiernas-Gallinero, MD

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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.

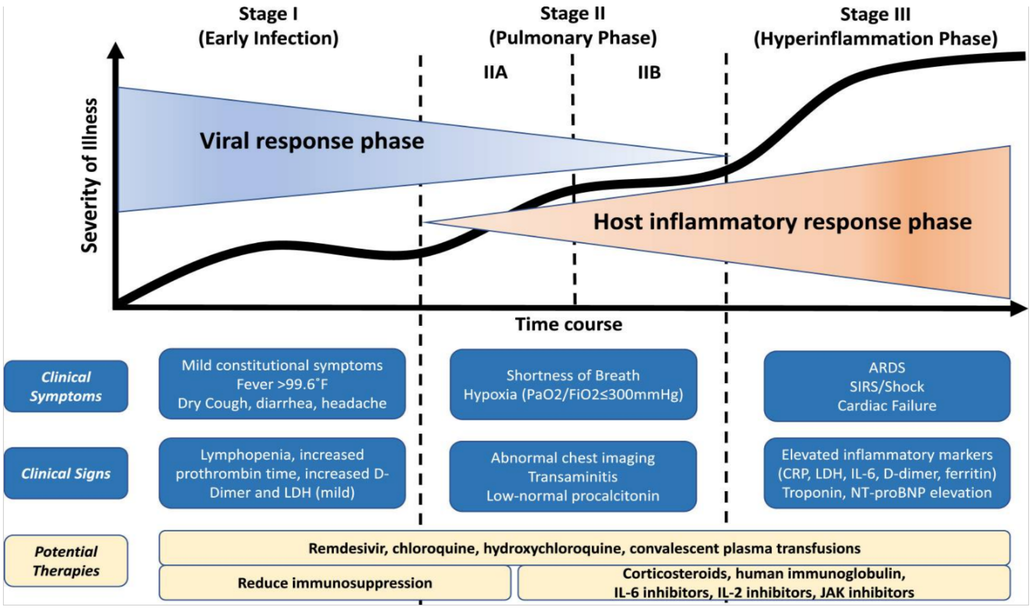

Figure 1. Classification of COVID-19 Disease States and Potential Therapeutic Targets
The figure shows 3 escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome, CRP=C-reactive protein; 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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NEW & UPDATED IMMUNOMODULATORS REVIEWED FOR THE 4.2 VERSION

1. PIRFENIDONE

Eileen Simone Alikpala Cuajunco, MD

Introduction

Pirfenidone is an anti-fibrotic drug used to treat fibrotic diseases. Severe cases of COVID-19 often show an extensive presence of pulmonary fibrotic tissue, and cytokines and growth factors causing pulmonary fibrosis are strongly increased in patients with COVID-19. Mediators such as transforming growth factor-β (TGF-β), Vascular endothelial growth factor (VEGF), Interleukin-6, and tumor necrosis factor-α (TNF-α) vascular dysfunctions can lead to the progression of fibrosis.[1] The pathophysiological, biological, and molecular characteristics of SARS-CoV-2 brings into light pirfenidone as monotherapy or in combination with anti-inflammatory drugs. This concept may also be effective as a post-infection medication in patients with residual pulmonary fibrotic damage.[2,3]

Mechanism of Action

Pirfenidone shows pleiotropic properties in terms of antifibrotic, anti-inflammatory, and antioxidant effects.[1] Its use could result in apoptosis inhibition, downregulation of ACE receptor expression, decrease in inflammation resulting in the protection of pneumocytes from COVID-19 invasion and cytokine storm.[4]

1. **Anti-inflammatory effects:** Pirfenidone inhibits TNF-α secretion and decreases many other inflammatory cytokines.[5] Li et al. showed that pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking nucleotide-binding oligomerization domain-like receptor with pyrin domain 3 (NLRP3) inflammasome activation and subsequent IL-1β secretion.[6]

2. **Anti-fibrotic effects**: Pirfenidone significantly inhibits TGF-β1 induced fibronectin synthesis which results in the suppression of adhesion molecule expression.[7]

3. **Anti-oxidant effect and lipid peroxidation:** Cytoskeletal damage and lipid peroxidation are the other destructive effects of inflammation and severe oxidative stress due to cytokine storm. The antioxidant character of pirfenidone makes it potent for the treatment of hyperimmune response.[8]

4. **Down regulation of ACE receptor expression:** Pirfenidone inhibits the angiotensin II type 1 receptor (AT1R)/phospho-p38 mitogen-activated protein kinase (p38 MAPK) pathway, decreased angiotensin-converting enzyme (ACE), angiotensin II, and angiotensin II type 1 receptor expression, and strongly enhanced liver X receptor-α expression. These results indicate that the cardioprotective effects of Pirfenidone [9]

Clinical Studies

*Ongoing NCT04653831***:** Treatment with Pirfenidone for COVID-19 related Severe ARDS[10]

Recommended Dose

It is available as an oral drug (Brand name: Esbriet) and given for Idiopathic Pulmonary Fibrosis as follows:[11]

- Days 1-7: 267 mg PO TID (801 mg/day)
- Days 8-14: 534 mg PO TID (1602 mg/day)
- Day 15 and thereafter (maintenance): 801 mg PO TID; not to exceed 2403 mg/day

An inhaled formulation of pirfenidone is under evaluation in patients with COVID-19 (NCT04282902). Pirfenidone should be avoided if patients have an estimated glomerular filtration rate of less than 30 mL/min per 1·73 m^2.

Adverse Effects

Pirfenidone should be taken with food to help reduce dizziness and gastrointestinal side effects: nausea, vomiting, diarrhea, constipation, indigestion, stomach wind, stomach discomfort or pain, loss of taste perception, loss of appetite. Other side effects: headache, drowsiness, difficulty sleeping, tiredness, weakness, weight loss, flush, chest pain, breathlessness, cough, muscle or joint pain, rash and itching, reddening or drying of skin.[12]

Conclusion

Pirfenidone may have a therapeutic potential to prevent or reduce fibrotic lung lesions of the ongoing COVID-19 infection, or in patients already healed but with fibrotic consequences.

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2. ANTIVIRALS

Eden P. Macalalag, MD, Melissa Anne G. Rapadas-Aguirre, MD, Ma. Stella G. Paspe, MD, Ivy June Minerva Soriano, MD

Antiviral drugs are a class of medicines particularly used for the treatment of viral infections. Anti-viral drugs that directly target the viruses include the inhibitors of virus attachment, inhibitor of virus entry, uncoating inhibitors, polymerase inhibitors, protease inhibitors, inhibitors of nucleoside and nucleotide reverse transcriptase and inhibitors of integrase.[1]

Most antivirals work by inhibiting viral replication and/or release of viral particles by the host cell thereby decreasing the quantity that can trigger the initial anti-viral response. This reaction is generated by the innate immune system and involves the secretion of interferons and other pro-inflammatory cytokines that may lead to a dysregulated immune response seen in moderate or severe COVID-19 infections. Although, generally viewed as anti-infective agents, antivirals, via inhibition of viral replication maybe considered as immunomodulators by themselves. Fewer virions to be contained and controlled by the immune system would need a less explosive and more optimally calibrated cytokine secretion.[1] 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.[2]

Host-targeting antivirals are compounds that regulate the function of host factors which are crucial for virus replication. Interferon (IFN) is one of the most crucial molecules in the innate immune response and acts as the primary switch for initiating antiviral immunity in vertebrates. Upon being infected by a virus, host cells produce and secrete type I (mainly IFN-alpha and IFN-beta) and type II (Interferon-gamma). These secreted IFNs interact with the membrane-anchored IFN receptors (IFNARs) and subsequently stimulate and upregulate the expression of hundreds of IFN-stimulated genes (ISGs) to inhibit the replication of viruses.[3] The discussion on interferons can be found in another section.

Some antiviral agents like umifenovir (Arbidol) have been reported to produce more direct immunomodulatory responses by inducing interferon production and stimulating phagocytic function.[4]

Antiviral agents have also been included in large multicenter, international clinical trials. However, the adaptive quality of these studies enables them to discontinue a certain drug if there is no evidence of beneficial effects. Such is the case for the removal of lopinavir/ ritonavir in the in the World Health Organization's "Solidarity Trial", RECOVERY Trial in the United Kingdom, ASCOT trial in Australia, and the ACTT trial by NIAID. Furthermore, preliminary results from various studies and systematic review and meta-analysis have been published since the last version of this document.

A. REMDESIVIR/ RDV/ GS-5734

Introduction

Remdesivir is an investigational drug with broad-spectrum activities against MERS and SARS in vitro and has been tested for Ebola.[1] It is currently being investigated in clinical trials and is also available through expanded access and compassionate use for certain patient populations.

Mechanism of Action

Remdesivir, a nucleotide analogue 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.[2]

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.[3]

Clinical Trials

In the COVID-19 Living Report, clinical improvement at day 28 (RR 1.06, 95% CI 0.99 to 1.13) and all-cause mortality (RR 0.91, 95% CI 0.75 to 1.11) for mild to severe COVID-19 patients given remdesivir compared to placebo or standard of care were inconclusive.[4] Included in this living report is the study of Wang on severe COVID-19 patients which showed that there was no difference in time to clinical improvement (median time 21 days vs. 23 days; HR 1.23, 95% CI 0.87 to 1.75) nor 28-day mortality among severe COVID-19 patients given remdesivir compared to placebo.[5]

In a double-blind, randomized, placebo-controlled trial (ACTT-1) of hospitalized COVID-19 patients, remdesivir reduced the time to recovery in patients who required supplemental oxygenation at enrollment [recovery rate ratio (RRR) 1.45, 95% CI 1.18 to 1.79] compared to placebo. The observed benefit in the reduced time to recovery was seen among those with severe COVID-19 but not mild or moderate COVID-19. There was no observed difference in time to recovery between remdesivir and placebo in patients on high-flow oxygen or noninvasive ventilation at enrollment (RRR 1.09, 95% CI 0.76 to 1.57).[6]

In a randomized, double-blind, placebo-controlled trial (ACTT-2) of hospitalized COVID-19 patients the combination of baricitinib and remdesivir compared to remdesivir alone was evaluated. It showed that among those who received the combination treatment of baricitinib and remdesivir recovered a median 1 day faster compared to those on remdesivir alone (7 days vs 8 days; RRR 1.16, 95% CI, 1.01 to 1.32). Faster recovery was observed among patients on high-flow oxygen or noninvasive mechanical ventilation who received the combination treatment (median, 10 days vs 18 days; RRR 1.51, 95% CI 1.10 to 2.08).[7]

An observational study in pregnant and postpartum women requiring invasive ventilation showed that the use of remdesivir resulted in a decrease in the level of oxygen requirement. Remdesivir was well tolerated by pregnant women with a low incidence of serious adverse events.[8]

Recommendations of governing bodies

1) World Health Organization reviewed the Solidarity trials of four repurposed antiviral drugs namely remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon beta-1a in hospitalized COVID-19 patients and showed that these drugs had little or no effect as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. No recommendation was made.[9]
2) The National Institutes of Health COVID-19 Treatment Guideline Panel stated that there is insufficient evidence to recommend for or against treating patients with mild to moderate COVID-19 (i.e., non-hospitalized patients or hospitalized patients that do not require supplemental oxygen). The Panel also recommends the combination of dexamethasone and remdesivir for patients who require increasing amounts of oxygen supplement.[10]

3) The Philippine COVID-19 Living Recommendations suggests against the use of remdesivir in patients with COVID-19 infection who have O2 saturation ≥94% and do not require oxygen supplementation and also against its use in patients who are already on invasive mechanical ventilation. However, it recommended the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation < 94% and/or requiring oxygen supplementation. They also recommended that for patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued.[11]

As of May, 2021 there are 45 registered clinical studies on remdesivir, with 25 studies, currently recruiting patients.

Recommended Dose

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.[12]

NIH COVID-19 Treatment Guidelines Panel Recommendations [12,13]

For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg)

- For Patients Who Are Not Mechanically Ventilated and/or on ECMO:
  - Remdesivir 200 mg IV over 30–120 minutes on Day 1, followed by remdesivir 100 mg IV on Day 2 through Day 5
  - In patients who have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days.
- For Mechanically Ventilated Patients and/or Patients on ECMO:
  - Remdesivir 200 mg IV over 30–120 minutes on Day 1, followed by remdesivir 100 mg IV on Day 2 through Day 10

Suggested Dose in EUA[a] for Hospitalized Pediatric Patients Weighing 3.5 kg to < 40 kg or Aged < 12 Years and Weighing ≥3.5 kg

- For Patients Weighing 3.5 kg to < 40 kg:
  - Remdesivir 5 mg/kg IV over 30–120 minutes on Day 1, followed by remdesivir 2.5 mg/kg once daily starting on Day 2
  - For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days.
  - For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days.
- For Patients Aged < 12 Years and Weighing ≥40 kg:
  - Same dose as for adults and children aged >12 years and weighing >40 kg

Not Recommended

- If eGFR is < 30 mL/min

May need to be discontinued if ALT levels increase to >10 times the upper limit of normal and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.

[a] *The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to < 40 kg or aged < 12 years and weighing ≥3.5 kg.*

ALT = alanine transaminase; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration;

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.[5]

According to Goldman JD, et al, the most common adverse events were nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).[14]

Incidence of adverse events was similar among remdesivir and standard of care (RR 0.93, 95% CI 0.85-1.01). There were fewer serious adverse events in remdesivir group compared those who received standard of care alone (RR 0.60, 95% CI 0.38-0.96).[4]

Conclusion

A single large RCT showed reduced time to recovery among those with severe COVID-19 and oxygen supplementation given remdesivir compared to standard of care alone/placebo. Better clinical outcomes were noted with concomitant treatment with systemic steroids for patients on supplemental oxygen but not on high-flow or mechanical ventilation. Evidence on clinical improvement and all-cause mortality for remdesivir compared to standard of care or placebo for COVID patients are still inconclusive for mild to moderate COVID-19.

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B. RIBAVIRIN/RBV

Introduction

Ribavirin is a broad-spectrum antiviral drug that hinders viral replication and spread.[2] It is primarily used for Respiratory Syncytial Viral infection, Influenza virus and chronic Hepatitis C.[5,6] A study on patients with SARS treated with LPV/r and ribavirin had a lower risk of ARDS and death compared with monotherapy.[7] Most published international recommendation guidelines for the treatment of COVID-19 have not included ribavirin in their reports on treatment for COVID-19.[8]

Mechanism of Action

In a review of nucleotide inhibitors, RBV was found to cause human Coronavirus eradication in vitro.[9] For SARS patients, it is effective as prophylaxis and as treatment when combined with IFN-b.[10] Ribavirin has also been found to reduce macrophage activation, diminish Th2 cytokine production and preserve Th1 cytokine production among patients with hepatitis C virus.[11]

Clinical Trials

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 multicenter, prospective, open-label, randomized, phase 2 trial in adults with COVID-19 was done in Hong Kong that evaluated the safety and efficacy of ribavirin combined with LPV/r + interferon. The control group received LPV/r only. The median number of days from symptom onset to start of study treatment was 5 days; the primary outcome was time to achieve a negative RT-PCR. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days) with a hazard ratio of 4.37 ([95% CI 1.86–10.24], p=0·0010). Adverse events included self-limited nausea and diarrhea with no difference between the two groups. Early triple antiviral therapy was safe and superior to LPV/r alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.[13]

A multicenter, retrospective cohort study of COVID-19 inpatients admitted to 4 hospitals in China was conducted to assess the effectiveness and safety of ribavirin and interferon-α (RBV/IFN-α) therapy in COVID-19 patients. Patients were divided into 2 groups according to their exposure to RBV/IFN-α therapy within 48 h of admission. RBV/IFN-α therapy was not associated with progression from non-severe into severe type or with reduction in 30-day mortality. However, it was associated with a higher probability of hospital stay >15 days compared with no RBV/IFN-α therapy. They also mentioned that the inappropriate timing of IFN-α might have prolonged the patients' hospital stay.[14]

A single-center, retrospective cohort study was conducted, and it included patients diagnosed with laboratory-confirmed SARS-CoV-2 infection. It compared ribavirin therapy versus supportive therapy only for patients with severe COVID-19. In this study the results showed that the negative conversion time for SARS-CoV-2 test in patients who received ribavirin was 12.8 ± 4.1 days compared with 14.1 ± 3.5 days in the control group (p = 0.314). The use of ribavirin also did not improve the mortality rate mortality rate compared to the control group [17.1% (7/41) in ribavirin group and 24.6% (17/69) in control group]. [15]

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

There are 7 registered clinical trials, with 2 of which are currently recruiting.

Recommended dose

500 mg intravenous infusion for adults 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir for not more than 10 days.[17]

Adverse Effects

Ribavirin can reduce hemoglobin concentration.[5] It is contraindicated in patients with severe hepatic and renal impairment and in known or suspected pregnant women.[16]

Conclusion

The inconclusive efficacy data with ribavirin and its substantial toxicity suggest that it has limited value for treatment of COVID-19. If used, combination therapy likely provides the best chance for clinical efficacy.

C. <u>FAVIPIRAVIR / T-705/ FAVIPIRA/ FAVILAVIR</u>

Introduction

Since the last edition of this paper, a number of studies have been published. Several countries, including China, India and Russia, have now approved its use for COVID-19.

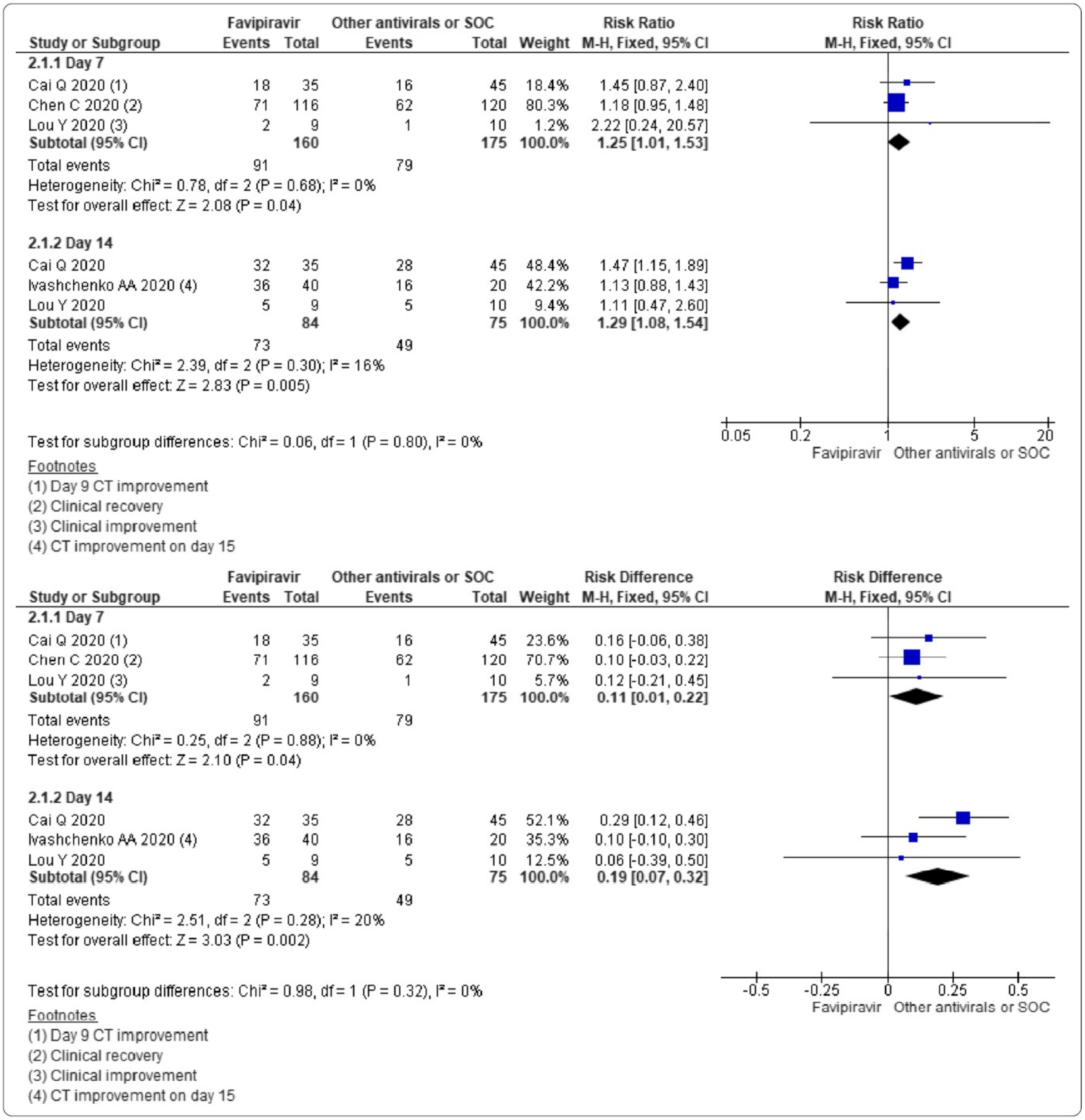
Mechanism of Action

In an vitro study on SARS-Cov-2, favipiravir acts as a nucleoside analogue inhibiting the RNA-dependent RNA polymerase of the SARS-CoV-2 causing chain termination, slowed RNA synthesis and lethal mutagenesis. This causes decreased viral replication may possibly prevent excessive release of proinflammatory cytokines.[18]

Clinical Trials

An open-label non-randomized study in China comparing favipiravir + interferon-a inhalation and LPVr + interferon-a inhalation showed that patients in the favirapir group had significantly shorter viral clearance time compared to the LPV/r group ($P < 0.001$). There was no significant difference in the improvement rates of chest CT changes after days 4 and 8 of treatment; but the improvement rates after day 14 in the FPV arm were significantly higher than those in the LPV/r arm (91.4% versus 62.2 %, 32/35 versus 28/45, $P = 0.004$) [19]

A meta-analysis involving 9 clinical studies with a total of 875 COVID-19 patients showed significant improvement on the 7th (RR 1.25, 95% CI 1.01 to 1.53) and 14th day (RR 1.29, 95% CI 1.08 to 1.54) of treatment when compared to standard of care day 14 as seen in Figure 1. In terms of viral clearance, clinical deterioration rate, oxygen support requirements and non-mechanical ventilation, there was no statistically significant difference when compared with standard of care or the other antiviral group. (Figures 2-4) The limitation of the meta-analysis is the moderate to considerable heterogeneity of the studies included.[20]



Study or Subgroup	Favipiravir Events	Favipiravir Total	Other antivirals or SOC Events	Other antivirals or SOC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Day 7						
Cai Q 2020 (1)	18	35	16	45	18.4%	1.45 [0.87, 2.40]
Chen C 2020 (2)	71	116	62	120	80.3%	1.18 [0.95, 1.48]
Lou Y 2020 (3)	2	9	1	10	1.2%	2.22 [0.24, 20.57]
Subtotal (95% CI)		**160**		**175**	**100.0%**	**1.25 [1.01, 1.53]**
Total events	91		79			
Heterogeneity: Chi² = 0.78, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
2.1.2 Day 14						
Cai Q 2020	32	35	28	45	48.4%	1.47 [1.15, 1.89]
Ivashchenko AA 2020 (4)	36	40	16	20	42.2%	1.13 [0.88, 1.43]
Lou Y 2020	5	9	5	10	9.4%	1.11 [0.47, 2.60]
Subtotal (95% CI)		**84**		**75**	**100.0%**	**1.29 [1.08, 1.54]**
Total events	73		49			
Heterogeneity: Chi² = 2.39, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 2.83 (P = 0.005)						

Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%

Footnotes
(1) Day 9 CT improvement
(2) Clinical recovery
(3) Clinical improvement
(4) CT improvement on day 15

Study or Subgroup	Favipiravir Events	Favipiravir Total	Other antivirals or SOC Events	Other antivirals or SOC Total	Weight	Risk Difference M-H, Fixed, 95% CI
2.1.1 Day 7						
Cai Q 2020 (1)	18	35	16	45	23.6%	0.16 [-0.06, 0.38]
Chen C 2020 (2)	71	116	62	120	70.7%	0.10 [-0.03, 0.22]
Lou Y 2020 (3)	2	9	1	10	5.7%	0.12 [-0.21, 0.45]
Subtotal (95% CI)		**160**		**175**	**100.0%**	**0.11 [0.01, 0.22]**
Total events	91		79			
Heterogeneity: Chi² = 0.25, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
2.1.2 Day 14						
Cai Q 2020	32	35	28	45	52.1%	0.29 [0.12, 0.46]
Ivashchenko AA 2020 (4)	36	40	16	20	35.3%	0.10 [-0.10, 0.30]
Lou Y 2020	5	9	5	10	12.5%	0.06 [-0.39, 0.50]
Subtotal (95% CI)		**84**		**75**	**100.0%**	**0.19 [0.07, 0.32]**
Total events	73		49			
Heterogeneity: Chi² = 2.51, df = 2 (P = 0.28); I² = 20%						
Test for overall effect: Z = 3.03 (P = 0.002)						

Test for subgroup differences: Chi² = 0.98, df = 1 (P = 0.32), I² = 0%

Footnotes
(1) Day 9 CT improvement
(2) Clinical recovery
(3) Clinical improvement
(4) CT improvement on day 15

Figure 1. Forest plot for risk ratios and risk differences regarding FVP in addition to standard of care effectiveness for clinical improvement compared with other antivirals or SOC[20]

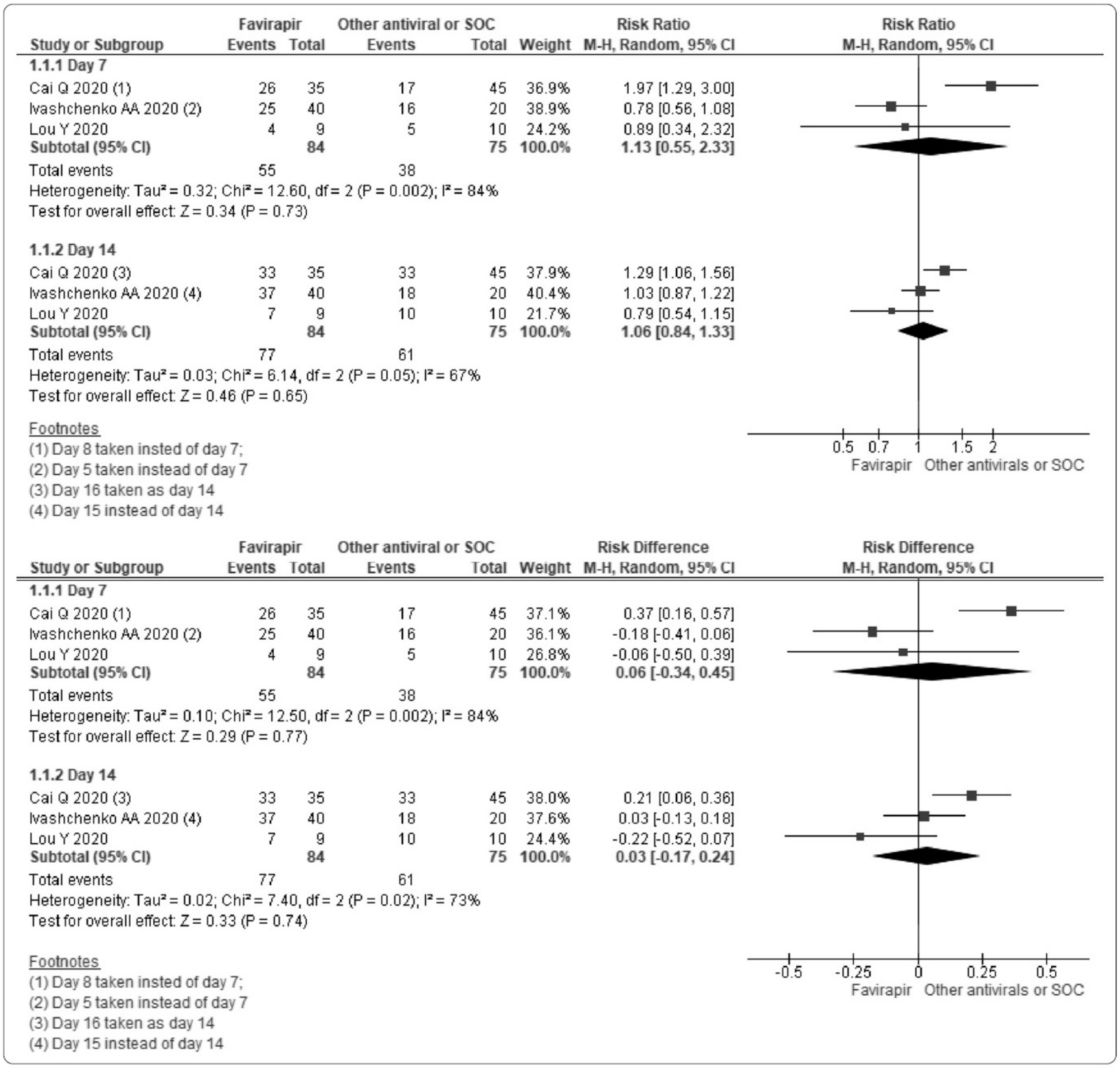


Figure 2. Forest plot for risk ratios and risk differences regarding FVP in addition to SOC effectiveness for viral clearance compared with other antivirals or SOC[20]

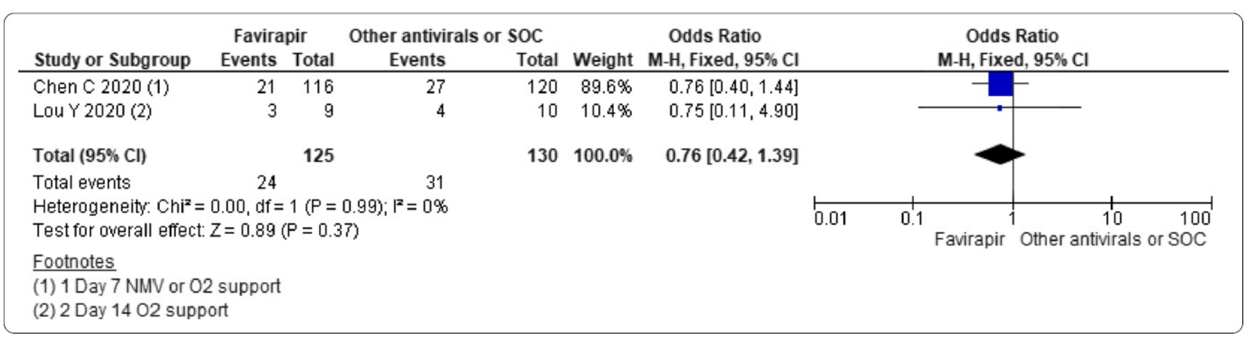


Figure 3. Forest plot for odds ratios requiring oxygen support or non-invasive ventilation among FVP groups versus other antivirals or SOC group[20]

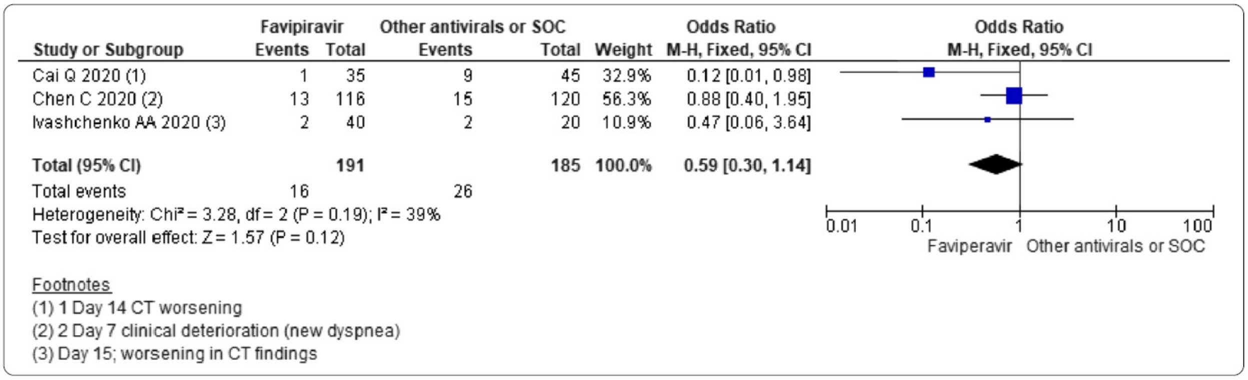


Figure 4. Forest plot for odds ratio regarding clinical deterioration among FVP group vs other antivirals[20]

Published results of a phase 3 clinical trial in India involving 150 patients with mild to moderate COVID-19 showed median time to clinical cure among symptomatic patients was significantly faster with favipiravir at 3 days compared with control at 5 days (p= 0.030). Among patients who deteriorated and required O2 support, those receiving favipiravir had a significantly longer median time for use of oxygen at 5 days versus 2 days for those who received standard care (p=0.034). There was no significant difference in the median time to hospital discharge (p = 0.108) and viral clearance of oral shedding among the two groups (p= 0.129).[21]

In a randomized trial of 89 patients with asymptomatic to mildly symptomatic COVID-19, administration of Favipiravir was associated with lesser time to defervescence, and a significant improvement in fever was observed on day 2 of favipiravir therapy, compared with no therapy (aHR, 1.88; 95% CI, 0.81 to 4.35) however no significant difference in viral clearance was noted in the first 6 days (aHR 1.42; [95% CI], 0.76 to 2.62).[22]

A multicenter open labeled clinical trial of 424 COVID-19 patients, favipiravir therapy had no influence on ICU admission in comparison with lopinavir/ritonavir. It did not reduce the need for intubations or in-hospital mortality, nor did it improve the length of hospital stay and overall clinical recovery of patients.[23]

In another multicenter randomized controlled study with 96 participants with mild to moderate COVID-19 patients, there was no statistical significance in the mean duration of stay, need for mechanical ventilation, oxygen saturation lower than 90% and death in the favipiravir group versus hydroxycholoroquine group. [24]

Recommendations

In the latest NIH COVID-19 treatment guidelines, favipiravir was not included. However, the use of favipiravir as an empirical treatment is included in the guidelines of Thailand, UAE, and Malaysia and is used with or without HCQ/CQ in severe cases, while it is not recommended in Nigeria unless in a clinical trial setting.[25] This drug is also used for the treatment of COVID-19 in the elderly and children in Saudi Arabia.[26]

Recommended dose and duration of treatment[26]

Adults:

Oral favipiravir 1800 mg BID loading dose on day 1; 800 mg BID for 7-10 days.

Pediatric Dosing given for 7 – 10 days:

For 10-15 kg: Loading Dose: 1 tablet PO BID for day one (maximum 400 mg/day), then half tablet (100 mg) PO BID (maximum 200 mg/day)

For 16-21 kg: Loading Dose: 2 tablets PO BID day one (maximum 800 mg/day), then one 1 tablet PO BID (maximum 400 mg/day)

For 22-35 kg: Loading Dose: 3 Tablets PO BID for day one (maximum 1200mg/day), then 1 tablet PO TID (maximum 600 mg/day)

For 36-45 kg: Loading Dose: 3 tablets PO BID for day one (maximum 1600mg/day), then 2 tablets PO BID (maximum 800 mg/day)

For 46-55 kg: Loading Dose: Five tablets PO BID for day one (maximum 2000mg/day), then 2 tablets qAM, 3 Tablets qPM (maximum 1000 mg/day)

For >55 kg: Can use adult dosing if age ≥16 years, if age <16years use dosing of 46-55 kg range

Adverse Effects

Some of the adverse effects are raised serum uric acid, abnormal liver function tests, psychiatric symptom, GI disturbance. Most were mild to moderate and transient. However, these were tolerable and was not statistically significant compared with standard of care (OR 0.69, 95% CI 0.13 to 3.57)[20]. It is contraindicated for known or suspected pregnant women and lactating women [19, 27]

Drugs that may potentially cause drug interactions with favipiravir are aldehyde oxidase inhibitors such as selective estrogen receptor modulators (raloxifene, tamoxifen, estradiol), H2 receptor antagonist (cimetidine) calcium channel blockers (felodipine, amlodipine, and verapamil), anti-arrhythmic drugs (propafenone) and tricyclic antidepressant amitriptyline.[4]

Conclusion

Studies on favipiravir seem to be promising for mild to moderate COVID-19 with pediatric dosing established in other countries. But more clinical trials should be done for a more definitive role of favipiravir in the treatment of COVID-19.

D. 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.[28]
China has added Umifenovir as an antiviral option in their treatment protocol for COVID- 19.[27]

Mechanism of Action

Umifenovir has also been reported to produce an immunomodulatory response by inducing interferon production and stimulating the phagocytic function of macrophages and prevents the fusion of the viral membrane with the endosome after endocytosis.[28]

In vitro studies on umifenovir showed that it can bind lipid membranes and may alter membrane configuration of the cytoplasm or the endosome, which are crucial for viral attachment and fusion. These results suggested that umifenovir impeded not only viral attachment, but also release of SARS-CoV-2 from intracellular vesicles.[29, 30]

Clinical Trials

A systematic review and meta-analysis on the efficacy and safety of umifenovir for COVID-19 involved 12 studies with a total of 1052 patients. It showed no significant difference of conversion time from positive to negative SARS-COV-2 nucleic acid via PCR between the umifenovir vs the control group. The umifenovir group was not associated with a higher negative rate on day 7 (RR:1.09; 95% CI: 0.91 to 1.31), however showed increase negative rate on day 14 (RR:1.27; 95% CI 1.04 to 1.55). Umifenovir was also not associated with the incidence of critically ill patients and death. Furthermore, this meta-analysis showed no significant association between umifenovir and symptom alleviation of cough and fever on day 7, and length of hospital stay. This drug was also found to be safe among patients with COVID-19.[31] The limitation of the said meta-analysis was the low quality and certainty of evidence and heterogeneity of the studies included.

In a systematic review on antivirals involving 16 studies, umifenovir monotherapy did not influence shortening the time of conversion from positive to negative COVID-19 nucleic acid in respiratory specimens compared to lopinavir-ritonavir. Furthermore, there was no reported improvement in symptoms. In patients treated with umifenovir in combination with lopinavir-ritonavir, 94% of patients tested negative for SARS-CoV-2 in comparison to 53% in the lopinavir-ritonavir monotherapy group at day 14. Moreover, improvement in chest CT were also noted after 7 days (69% vs. 29%). A small sample size on the analyzed studies was the limitation in this systematic review.[32]

Published results from an open label, randomized controlled trial of umifenovir versus lopinavir/ritonavir among 104 hospitalized COVID-19 patients, showed the duration of hospitalization was significantly less in the umifenovir group (7.2 vs 9.6 days; $p = 0.02$). Radiologic findings were also significantly different after 30 days of admission in the umifenovir group (CT scan $p= <0.004$; CXR $p= <0.001$) Other findings with statistical difference in favor of the umifenovir group were peripheral oxygen saturation, WBC and neutrophil count, ESR and blood potassium ($P = <0.001$). [33]

Recommendations

Currently, there are no recommendation to use Umifenovir in treating for COVID-19 patient form the CDC or the NIH.

The use of umifenovir, in combination with either hydroxychloroquine/ Mefloquine or recombinant IFN-a, is included in Russian Ministry of Health treatment protocol for the management of COVID-19.[34]
Umifenovir is included in the Chinese Clinical Guidance for COVID-19 pneumonia diagnosis and treatment, 7th edition.

Recommended dose and duration of treatment [34]

Umifenovir 200mg every 6 hours for 5 days, in combination with either hydroxychloroquine, Mefloquine or recombinant IFN-a

Arbidol 200mg, 3x a day, for not more than 10 days

Adverse Effects

Umifenovir was shown to be safe, even for use in pregnant women and showed no teratogenic effect. Combination LPVr + umifenovir induced liver damage in about 50% of treated patients.[35] The usage over several days to one month was also well tolerated. Some of the reported side effects are diarrhea, dizziness, jaundice and elevated serum transaminase, occasional bradycardia.[28]

Conclusion

Published reports on the role of umifenovir for COVID-19 is varied. Nevertheless, several ongoing clinical trials evaluating the efficacy of umifenovir for COVID-19 may clarify this issue However, its good safety profile makes it a promising drug for the treatment of COVID-19.

E. <u>OSELTAMIVIR</u>

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.[36] 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.[37] In Egypt, Oseltamivir is included in their standard of care treatment for confirmed COVID-19 patients.[38]

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.[36] 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.[39]
However, recent in vitro studies showed oseltamivir to have no antiviral effect against COVID-19.[40]

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.[6, 41] A retrospective, single center case series of the 138 consecutive hospitalized patients in Wuhan, China, in which most of the patients received oseltamivir, reported that no positive outcomes were observed after receiving antiviral treatment with oseltamivir.[42]

In a retrospective cohort, multicenter study in Egypt with 40 children aged 8mos – 17yrs with asymptomatic to mild COVID-19 showed that there was no statistical difference noted between patients given oseltamivir alone and a combination of oseltamivir and hydroxychloroquine ($p=0.977$).[43]

Several clinical trials are still evaluating the effectiveness of oseltamivir in treating SARS-CoV-2 infection, mostly in combination with other antivirals and medications.

Recommendations

Currently, there are no recommendation form the CDC or the NIH to use oseltamivir in treating COVID-19 patients. The Egyptian National Guidelines for COVID-19 recommends its use for asymptomatic, mild to moderate and severe cases of COVID 19 patients in combination with other medications.[44] The Brazilian task force / consensus guideline for the treatment of COVID-19, strongly recommends against the use of oseltamivir for the treatment of COVID-19 patients with no suspected influenza coinfection.[45]

Recommended dose and duration of treatment [44]

Oseltamivir 75mg PO every 12 hours for asymptomatic patients
Oseltamivir 150mg PO every 12 hours for 5 days for mild to moderate cases
Oseltamivir 150mg PO every 12 hours for 10 days for severe cases

Adverse Effects

Oseltamivir adverse effects reported are nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children.[36]

Conclusion

Published studies on oseltamivir for COVID-19 are all observational and showed no improvement in clinical outcomes with the treatment.

F. <u>MOLNUPIRAVIR (MK-4482; EIDD-2801; NHC)</u>

Introduction

Monlupiravir an investigational, orally administered ribonucleoside analog that inhibits the replication of multiple RNA viruses including SARS-CoV-2, It has also been shown to be active in several preclinical models of SARS-CoV-2, including for prophylaxis, treatment, and prevention of transmission, as well as SARS-CoV-1 and MERS.[45]

Mechanisms of Action

Molnupiravir is quickly cleaved in plasma to EIDD-1931, which after distribution into various tissues, is converted to its corresponding 5′-triphosphate by host kinases EIDD-1931 5′-triphosphate is a competitive alternative substrate for the virally-encoded RNA-dependent RNA polymerase, and upon incorporation into nascent chain viral RNA induces an antiviral effect via viral error catastrophe.[46] It was shown to markedly inhibit SARS-CoV-2 replication in immunodeficient mice implanted with human lung tissue [47]
It was also shown to significantly reduce SARS-CoV-2 load in the upper respiratory tract and completely suppressed spread to untreated contact animals (ferrets).[48]

Clinical Trials

At the time of writing, there are a total of 4 (phase 2/3) ongoing recruitment of clinical trials assessing for the efficacy of molnupiravir in COVID-19 positive patients and its effects on viral shedding. There is 1 ongoing phase 2 study on safety tolerability (NCT04405570).[49]

Partial results from phase 2/3 trials (ClinicalTrials.gov: NCT04575584) showed molnupiravir to inhibit replication of the virus in treated patients at day 5 and day 10 compared to placebo. Moreover, partial results showed patients treated with molnupiravir had undetectable viral RNA at day 10 and 15.[46]

Recommended Dose (based on the phase 2/3 Clinical trial) [50]

Molnupiravir 200mg PO every 12 hrs for 5 days
Molnupiravir 400mg PO every 12 hrs for 5 days
Molnupiravir 800mg PO every 12 hrs for 5 days

Adverse Effects in healthy subjects

Molnupiravir was well tolerated at doses of 50 to 800 mg administered BID for 5.5 days and at single doses up to 1600 mg. The most frequently observed adverse events were headache and diarrhea. There were also no noted clinically significant findings in dose related trends in clinical laboratory, vital signs and electrocardiography [46]

Conclusion

Molnupiravir show potential in the eradication and prevention of transmission of the SARS CoV-2 based in animal studies. However, results of completed of clinical trials are needed to see the real-world evidence of this drug for patients with COVID-19.

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3. ASPIRIN

Cynthia Purificacion Ybiernas-Gallinero, MD

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), with Aspirin (ASA) as the prototype, are widely used first line minor pain and anti-pyretic medications used 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

Many of the studies suggest the possibility that pharmacologic actions of aspirin may play a role in enhancing the immune response to viral infections. Mechanisms proposed for ASA include prostaglandin (PG) inhibition via the cyclooxygenase pathway, altered leukocyte migration, activation of complement components, stimulation of monocytopoiesis, and induction of interferon. Since dual effects for ASA have been observed for several of these mechanisms, its role in modulating the immune response to viral infections is very complex and could lead to more studies and surveillance on its role in COVID-19 infections.[2]

COVID-19 has a high infection rate and mortality, and serious complications such as heart injury cannot be ignored. Cardiac dysfunction occurred in COVID-19 patients, but the law and mechanism of cardiac dysfunction remains unclear. The occurrence of progressive cytokine storm and coagulation dysfunction in severe and fatal cases of novel coronavirus pneumonia points out a new direction for reducing the incidence of severe and critically ill patients, shortening the length of duration in severe and critically ill patients and reducing the incidence of complications of cardiovascular diseases. Aspirin has the triple effects of inhibiting virus replication, anticoagulant and anti-inflammatory, but it has not received attention in the treatment and prevention of COVID-19 pneumonia.[3]

There is still a lack of effective drugs for the treatment of COVID-19, and the regularity and characteristics of myocardial injury in patients are unclear. In addition, prevention and treatment strategies for myocardial injury in COVID-19 patients have not been put on the agenda. The early use of aspirin in COVID-19 patients, which also has the effects of inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and reduce the incidence of cardiovascular complications.[3]

Aspirin has also been proposed as a treatment of Covid-19 on the basis of its antithrombotic properties as well.[4]

Clinical Studies

In this randomized, controlled, open-label platform trial (Recovery), several possible treatments were compared with usual care in patients hospitalized with Covid-19. Eligible and consenting adults were randomly allocated in a 1:1 ratio to either usual standard of care plus 150 mg aspirin once daily until discharge or usual standard of care alone using web-based (unstratified) randomisation with allocation concealment. The primary outcome was 28-day mortality. A total of 7351 patients were randomized to aspirin 150 mg once daily and compared with 7541 patients randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (17% aspirin vs 17%usual care; rate ratio 0.96 [95% confidence interval 0,89-1.04]; p=0.35).[4]

Recommended Dose

No recommended dose yet however in the ongoing trials of the use of Aspirin in COVID-19 treatment, 70 to 150 mg of ASA is used.

Adverse Effects

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.[5]

Conclusion

Present evidence does not indicate that aspirin may have a definite role in the treatment of COVID-19 cytokine storm. More clinical trials maybe need to establish its potential for management of severe COVID-19.

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4. CCR5 INHIBITOR (LERONLIMAB)

Alejandro P. Ortigas, MD

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

The US FDA published a categorical clarification on May 17, 2021 that Leronlimab did not support any clinical benefit based on the specific Clinical Trial application "CD10" (NCT 04343651) on mild to moderate COVID-19 disease of 86 patients and the larger "CD12" (NCT 04347239) Clinical Trial of 394 patients on its effect on severe symptoms of respiratory illness associated with COVID-19.[2] The desired primary and secondary endpoints of the complete clinical trial were not met. Although the drug manufacturer of Leronlimab has released publication of favorable results of the said drug, based on subsets or sub-groups of the clinical trial population, the FDA made a categorical statement to the effect that the published sub groups of Leronlimab manufacturer had no bearing and did not reflect the results of the complete study they specifically submitted (based on CD10 and CD12 trials) for FDA application.[2]

Leronlimab, as of the time of publication has a Compassionate Special Permit which may be requested from Philippine FDA by the physician concerned as an investigational drug.[3] In addition, it has 2 other pending Clinical Trials application (NCT 04901676 [4] and NCT 04901689[5]) with the US FDA. Recruitment to these trials have not yet commenced further information to these trials may be viewed at clinicaltrials.gov.

Recommended Dose:

700 mg subcutaneous once weekly for 2 weeks as indicated in the clinical trials. [6]

Adverse Effects

Some of the noted side effects were: headache, nausea, back pain, dizziness , diarrhea, vomiting, fatigue, injection site bleeding, injection site pain, injection site itching, sinusitis, pain in extremity, muscle and joint pain, viral respiratory infections, hypertension, difficulty breathing (which is rare).

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.[6]

Conclusion

Based on the latest USFDA statements and clinical trials, there is insufficient evidence to recommend leronlimab as an immunomodulator for severe COVID-19 pneumonia or cytokine storm. Further clinical trials demonstrating its efficacy are still needed.

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IMMUNOMODULATORS CURRENTLY UTILIZED IN THE MANAGEMENT OF COVID-19

1. CORTICOSTEROIDS

Maria Cristina R. Edquilag, MD, Frances M. Tan, MD

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

The use of corticosteroids for COVID-19 is largely based on the RECOVERY Trial. A total of 2104 patients were randomized to receive dexamethasone at 6mg per day for 10 days, either orally or via the intravenous route. Four thousand three hundred twenty-one patients were randomized to the usual care group. Dexamethasone reduced deaths in ventilated patients (0.65 (95% CI 0.48-0.88, pvalue = 0.0003) and in patients receiving oxygen (0.80 (95% CI 0.67-0.96, pvalue= 0.0021). There was no benefit among patients who did not require oxygen support (1.22 (95% CI 0.86-1.75, pvalue = 0.14). Overall, dexamethasone reduced 28-day mortality by 17% (0.83 (95% CI 0.74-0.92, pvalue = 0.0007), with a highly significant trend for those patients requiring ventilation.[6]

The WHO Rapid Evidence Appraisal for COVID-19 Therapies pooled data from 7 randomized controlled trials looked at the efficacy of corticosteroids among critically ill COVID-19 patients. 1703 subjects were included in the analysis. The primary outcome measure was all-cause mortality at 28 days after randomization, and the secondary outcome was investigator defined serious adverse events. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to the standard of care or placebo group. The summary OR was 0.70 (95% CI: 0.48 – 1.01, P=0.53) based on the random effects meta-analysis. This means that administration of systemic corticosteroids was associated with a lower 28-day all-cause mortality among patients with severe COVID-19 compared to those who received standard care or placebo. Likewise, there was no suggestion that the risk of serious adverse events was higher in the corticosteroid group.[7]

A systematic review and meta-analysis by Cano et al which included 73 comparative peer-reviewed articles, looked at the use of corticosteroids in severely ill COVID-19 patients. In these studies, 21.6% out of 21,350 COVID-19 patients received corticosteroids and most of these were low dose methylprednisolone. This review revealed that severely ill patients may benefit significantly from steroid use. The dose used for methylprednisolone was 1-2 mg/kg bolus followed by the same daily dose with gradual taper.[8]

In another meta-analysis of 44 studies, the over-all pooled estimate (observational and RCTs) showed a significant reduction in mortality in the corticosteroid group (OR 0.72 (95% CI 0.57-0.87). Fewer patients required mechanical ventilation in the corticosteroid group (pooled analysis (RR 0.71 (95% CI 0.54-0.97). Viral clearance, though, was longer in the steroid group (10-29 days) versus the standard care group (8-24 days). A trend toward more infections and antibiotics were associated with the corticosteroid group.[9]

The National Institutes of Health, in their COVID-19 treatment guidelines recommends the use of systemic corticosteroids for hospitalized COVID-19 patients who require the use of oxygen.[10]

The World Health Organization in their living guidance also stated that the use of systemic corticosteroids is recommended over not using systemic corticosteroids among patients with severe and critical COVID-19.[11]

The use of inhaled corticosteroids as treatment for early COVID-19 is also undergoing investigation. The STOIC (Steroids in COVID-19) study is an open label, parallel group, phase 2 randomized controlled trial of inhaled budesonide vs usual care, among adults within 7 days of onset of mild COVID-19 symptoms. The primary outcome was a COVID-19 related urgent care visit. There were 146 participants randomized into the budesonide group or the usual care group. Per protocol analysis showed that the primary outcome happened 10 out of 70 in the usual care group and 1 out of 70 in the budesonide group. In the intention to treat analysis, the primary outcome happened in 11 out of 70 in the usual care group and 2 out of 70 in the budesonide group. Clinical recovery was 1 day shorter in the budesonide group. [12]

In another multicenter, open label, multi-arm adaptive platform randomized controlled trial (the PRINCIPLE study) involved adults with suspected COVID-19. Participants were randomized to the following groups: Usual care, usual care with budesonide, usual care with other interventions. The primary outcome was hospitalization or death and time to first reported recovery. The interim analysis showed that time to self-reported recovery was shorter in the budesonide group compared to usual care. (hazard ratio 1.208 (95% BCI 1.076 – 1.356), the probability of superiority 0.999, estimated benefit, (95% BCI of 3.011(1.134 – 5. 41). Inhaled budesonide reduced time to recovery by a median of 3 days in people with COVID-19 at risk for adverse outcomes.[13]

Recommended Dose

Dexamethasone 6mg once daily (oral or IV) for ten days[10]

- If Dexamethasone is not available, the following may be used instead:
  - Prednisone 40mg once or twice daily
  - Methylprednisolone 32mg once or twice daily
  - Hydrocortisone 160mg 2-4 divided doses daily

NIH TREATMENT RECOMMENDATIONS ON THE USE OF CORTICOSTEROIDS FOR COVID-19[10]	
Disease Severity	**Recommendations**
Hospitalized, requires Oxygen (but does not require oxygen delivery through a high flow nasal device, non-invasive ventilation, invasive mechanical ventilation or ECMO	• **Dexamethasone* plus remdesivir** (e.g., for patients who require increasing amounts of oxygen); *or* • **Dexamethasone*** (e.g., when combination therapy with remdesivir cannot be used or is not available).
Hospitalized, requires oxygen delivered through a high-flow nasal device or non-invasive mechanical ventilation	• **Dexamethasone* alone; or** • A combination of **dexamethasone* plus remdesivir**.
Hospitalized, requires invasive mechanical ventilation or ECMO	• **Dexamethasone * alone** • Patients who initially received remdesivir monotherapy but progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be started and remdesivir should be continued until the treatment course is completed.

Dose for Inhaled Corticosteroids (ICS)

- Budesonide 400 ucg, 2 puffs 2x a day (STOIC study)[12]
- Budesonide 800 ucg, 2 x per day (PRINCIPLE study)[13]

Adverse Effects

Patients must be closely monitored and issues on hyperglycemia and electrolyte imbalances should be addressed when using oral or IV corticosteroids. One must also watch out for recurrence of inflammation, secondary infections, adrenal insufficiency and possibly drug-drug interactions. For ICS, oral thrush, dysphonia and throat irritation have been reported with its use and may be averted by gargling with water after administration.

Conclusion

The use of corticosteroids (particularly dexamethasone) as treatment (in combination with other therapies or by itself) for COVID-19 patients who are on supplemental oxygen or on mechanical ventilation is recommended by current treatment guidelines. It is NOT recommended for patients who do not require supplemental oxygen. 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.

The use of inhaled corticosteroids as early treatment for COVID-19 seems promising but data upon conclusion of the ongoing study is needed to make a more definite recommendation.

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2. ANTI-COAGULANTS (HEPARIN AND ITS DERIVATIVES)

Fatima Johanna T. Santos-Ocampo, MD and Roxanne C. Hao, MD

Introduction

Common laboratory abnormalities found in patients with COVID-19 not only include lymphopenia, elevation in lactate dehydrogenase, C-reactive protein, and interleukin-6 (IL-6) but also a procoagulant profile[1]. Characteristically, elevated concentrations of D-dimer, fibrin degeneration products and fibrinogen, and modestly low platelet counts are seen[2,3]. This type of profile is consistent with the increasing reports of widespread thromboses and disseminated intravascular coagulopathy in COVID-19 patients[4,5,6,7,8]. Lung involvement has been primarily noted and a strong association between coagulation dysfunction and ARDS was seen and is therefore considered as risk factors for mortality[9] .

Mechanism of Action

Among the anticoagulants that are in standard use and those that are under investigation, heparin is the most widely studied. At present, it is known to have at least four functions based on studies on different clinical conditions.

1. Anti-coagulant

Its anticoagulant properties come indirectly from its binding with antithrombin III (AT) and facilitating the subsequent inhibitory effect of AT on thrombin and activated factor X (factor Xa)[10,11]. It contains a unique pentasaccharide sequence that has an inhibitory action on factor Xa [12,13] recently synthesized for its targeted effect.

Types:

a. Unfractionated (UFH): short acting form, more suitable for patients with renal failure and acute coronary syndromes due to ease of hepatic clearance and better reversibility with protamine sulfate.
b. Low molecular weight Heparin (LMWH): long acting form such as enoxaparin, dalteparin and tinzaparin, with better adverse reaction profile than the UFH, less requirements for monitoring, higher bioavailability, and the potential for outpatient administration[14,15].
c. Fondaparinux: a synthetic analog of the pentasaccharide sequence of heparin necessary for AT binding as a prerequisite for Factor Xa inhibition and does not affect platelet function[16].

2. Anti-inflammatory

Heparin may indirectly, decrease inflammation by blocking the production of more fibrin as well as generation of degradation products. These substances can promote development of inflammation by activating neutrophils and monocytes, inducing the secretion of some inflammatory cytokines[17,18,19].

A possible direct anti-inflammatory action of heparin in COVID-19 is being considered as well. In a systematic review by Mousavi et al in 2015 [20], it was found out that heparin can decrease the level of inflammatory biomarkers. The review mainly involved the following conditions: asthma, inflammatory bowel disease, cardiopulmonary bypass, cataract surgery and acute coronary syndrome.

Heparin's anti-inflammatory effects may be attributed to its ability to bind with inflammatory cytokines[21] , inhibit neutrophil chemotaxis and leucocyte migration[22], sequester acute phase proteins such as P-selectin and L-selectin[23], induce cell apoptosis through tumor necrosis factor a and nuclear factor kβ pathways[21], affect histone methylation[24], affect mitogen-activated protein kinase and nuclear factor kβ signal pathways by inhibiting NF kappa β translocation from cytoplasm to the nucleus [25] and to neutralize complement factor C5a [26].

The neutralizing effect of heparin on C5a may also reduce its prothrombotic effect of upregulating tissue factor and PAI-1 expression by endothelial cells and monocytes.[27,28]

Other mechanisms for heparin's anti-inflammatory and anticoagulant effects have been previously studied in obstetric antiphospholipid antibody syndrome. Since a few case reports on COVID19 patients revealed significant levels of antiphospholipid antibodies[29,30] it would be worth investigating if heparin's therapeutic effects in such patients may be similar mechanistically to what is seen in patients with antiphospholipid antibody syndrome. To prove the theory, more high-quality evidence coming from RCT's are needed.

3. Endothelial protection

In rats, heparin has been shown to antagonize histones which, once released from damaged cells can injure endothelial cells. [31,32]

4. Anti-viral

In vitro studies have shown that heparan sulfate, an ubiquitous glycosaminoglycan on cell surfaces has been seen to interact with the SARS-Cov-2 spike protein and facilitate viral entry [33,34] It cleaves the S1 and S2 subunit of the S protein which exposes the S2 subunit, allowing it to bind with the ACE2 receptor. Heparin can bind to SARS-COV-2 and competitively inhibit [35] its attachment to the cell surface heparan sulfate. This property was seen in unfractionated heparin and was not appreciated in low molecular weight heparin[36].

Clinical Studies

Presently, randomized controlled trials on the use of anticoagulants in COVID 19 are still ongoing and have yet to report their results. There are three international trials covering 5 continents that aims to assess the benefit of full dose anticoagulants compared to a lower thromboprophylactic dose in moderately ill COVID-19 patients [37]. These are the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP); Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 (ACTIV-4) Antithrombotics Inpatient; and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC).

The American Society of Hematology came up with living guidelines on anticoagulation for thromboprophylaxis for patients with COVID -19[38]. The recommendations from the guidelines included the interim analysis of 3 ongoing randomized controlled trials on anticoagulation. They gave conditional recommendations for prophylactic dose of anticoagulation over intermediate-intensity or therapeutic dose anticoagulation for patients with COVID-19–related critical illness or acute illness who do not have confirmed or suspected VTE.

As of the date of publication of the current edition of this manuscript, there are no available updates on heparin's other functions described earlier (anti-inflammatory, anti-viral and endothelial protection) upon review of current literature. There are no specific recommendations on its use other than for thromboprophylaxis.

WHO gave conditional recommendations for prophylactic dose instead of intermediate or therapeutic dosing in patients admitted for COVID -19 (very low certainty)[39]. The Center for Disease Control and NIH, likewise, recommend prophylactic dose of anticoagulation for hospitalized non pregnant COVID-19 patients[37]. CDC further added that there is insufficient data to recommend for or against thrombolytics at higher doses than the prophylactic dose.

The Philippine Society of Vascular Medicine suggested prophylactic anticoagulation for the following conditions [40].

1) All hospitalized suspected, probable and confirmed COVID-19 patients with moderate to critical symptoms. Likewise, patients with mild symptoms but are admitted for other reasons are suggested to start prophylactic anticoagulation if with $\geq$4 Padua score (Table 1)
2) D-Dimer $\geq$ 1500ng/ml

Contraindications to prophylactic anticoagulation are the following:

1) Platelet $\leq$ 25 x 10^9/L
2) Active bleeding

Table 1: Padua Prediction Score for Risk of VTE in hospitalized medical patients

Items	Score
Active Cancer*	3
Previous VTE	3
Reduced mobility**	3
Known thrombophilia***	3
Recent ($\leq$1month) trauma and/or surgery	2
Elderly =/> 70 yrs	1
Heart and/or respiratory failure	1
Acute MI or ischemic stroke	1
Acute Infection &/0r rheumatologic disorder	1
Ongoing hormonal therapy	1
Obesity (BMI$\geq$ 30 kg/m2)	1

Padua score <4: Low risk for VTE
Padua score $\geq$4: High risk for VTE, prophylaxis is suggested

**Active cancer is defined as local or distant metastases and with chemotherapy or radiation in the previous 6 months*
***Reduced mobility is defined as anticipated bed rest with bathroom privileges for at least 3 days*
***Thrombophilic condition is defined as defects of antithrombin, protein C, or S, factor V leiden, G20210A prothrombin mutation, or antiphospholipid syndrome*

Recommended Dose

The American Society of Hematology recommends the prophylactic dosing of the following anticoagulants[38]:

- Apixaban 2.5mg, PO BID
- Bemiparin 3500 U, SC OD
- *Betrixaban 80 mg, PO OD**
- *Betrixaban 160 mg, PO OD**
- Dabigatran 220 mg, PO OD
- Dalteparin 5000 U, SC OD
- Enoxaparin 30 mg (3000 U), SC OD (for GFR 15-30)
- Enoxaparin 30 mg (3000 U), SC BID (for BMI $\geq$40 kg/m^2)
- Enoxaparin 40 mg (4000 U), SC OD
- Enoxaparin 40 mg (4000 U), SC BID (for BMI $\geq$40 kg/m^2)
- Fondaripanux 2.5mg, SC OD
- Unfractionated Heparin 5000 U, SC BID
- Unfractionated Heparin 5000 U, SC TID
- Unfractionated Heparin 7500 U, SC BID (for BMI $\geq$40 kg/m^2)
- Nadroparin 2850 U, SC q24h (post op general surgery)
- Nadroparin 5700 U, SC q24h (high risk medical patients $\geq$70kg)
- Nadroparin 3800 U, SC q24h (high risk medical patients $\leq$70kg or post op hip replacement surgery)
- Rivaroxaban 10mg, PO OD
- Tinzaparin 3500 U, SC OD
- Tinzaparin 4500 U, SC OD
- Tinzaparin 75 U/kg, SC OD

**Not available in the Philippines*

Adverse Effects

There is a 10-15% risk of significant bleeding in heparin use. [41,42] Risk factors for bleeding in the general population is older age, worse illness severity, longer hospital stay, decreased white blood cell and platelet counts which is commonly seen in COVID 19 patients. Another rare complication is heparin induced thrombocytopenia due to the development of antibodies to protein platelet factor 4.[43] However, this is not seen in the use of fondaparinux.

Conclusion

Although heparin has many immunomodulatory effects, use in COVID-19 patients is mainly for its anticoagulant property. Prophylactic dosing is considered to provide better outcomes.

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3. ANTI-INTERLEUKIN 6 (IL-6) or IL-6 INHIBITORS

Regina Dionisio Capulong, MD

Introduction

IL-6 and IL-1 are two of the main pro-inflammatory 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

Since the last update (September 20, 2020), there have been 10 clinical trials completed and published in peer-reviewed journals on IL-6 inhibitors for COVID-19.

The Cochrane living systematic review showed a decrease in the all-cause mortality at day 28 among those given tocilizumab compared to standard of care alone or placebo (RR 0.89, 95% CI 0.82 to 0.97) (Figure 1); however, there is little or no increase in the outcome of clinical improvement at D28 (RR 1.06, 95% CI 1.00 to 1.13) (Figure 2).[7] Included in this living systematic review were clinical trials on COVID-19 patients of different clinical severity. Seven of the RCT included in the Cochrane living systematic review reported the use of glucocorticoids at baseline.[8-14] Three trials had participants from the control arm receiving more steroids than the tocilizumab arm.[9,11,12] Two of the largest RCT, Randomised Evaluation of COVID-19 Therapy (RECOVERY) and Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), were included this living systemic review.

In the RECOVERY trial, a randomized, controlled, open-label, platform trial (RECOVERY]), moderate to critical COVID-19 patients (n=4116) with hypoxia and CRP ≥75 mg/L were randomized into either standard of care plus tocilizumab (8mg/kg) or standard of care alone. Majority of the patients (82%) were on corticosteroids prior to the start of randomization. Treatment with tocilizumab was associated with reduction in 28-day mortality (31% vs 35%; rate ratio 0.85, 95% CI 0.76 to 0.94) and likely to be discharged from hospital within 28 days (57% *vs* 50%; rate ratio 1. 22, 95% CI 1.12 to1.33).[10] Those who were on glucocorticoids and received tocilizumab had a significant reduction in mortality (risk ratio 0.79, 95% CI 0.70−0.89) compared to those who were not on corticosteroid (risk ratio 1.16 95% CI 0.91−1.48). The reduction in mortality among those on glucocorticoids and were given tocilizumab compared to those who were not on glucocorticoids was also shown in the sub-group analysis of 4 RCT in the Philippine COVID-19 Living Clinical Practice Guidelines.[15]

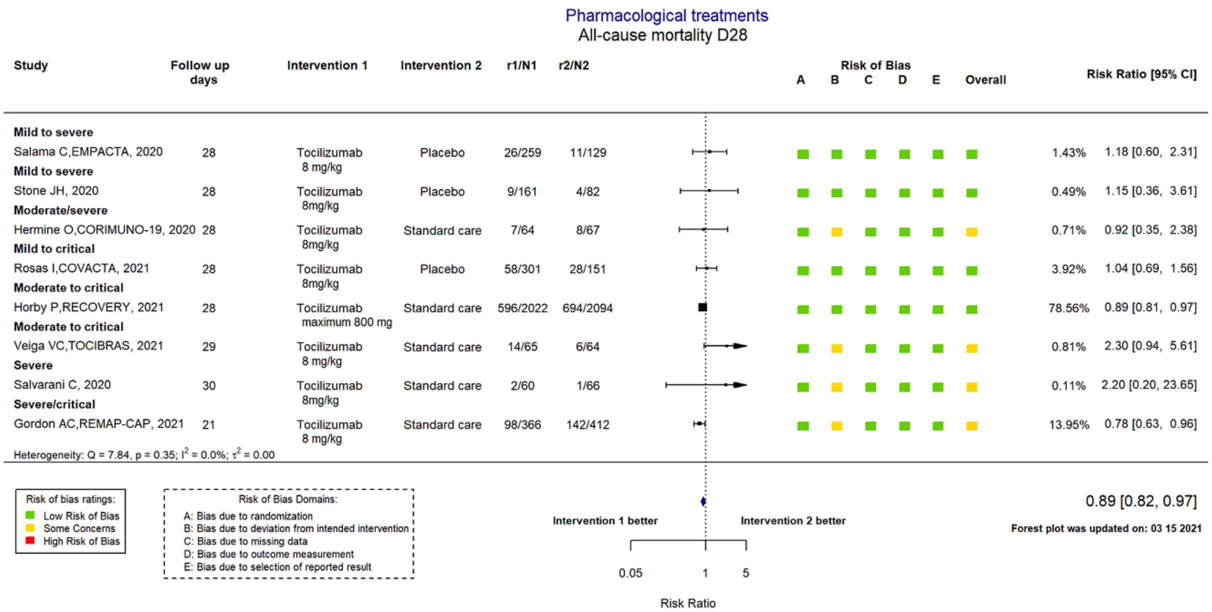

***Figure 1**. Forest plot showing all-cause mortality D28 on tocilizumab compared to standard of care/placebo* [7]

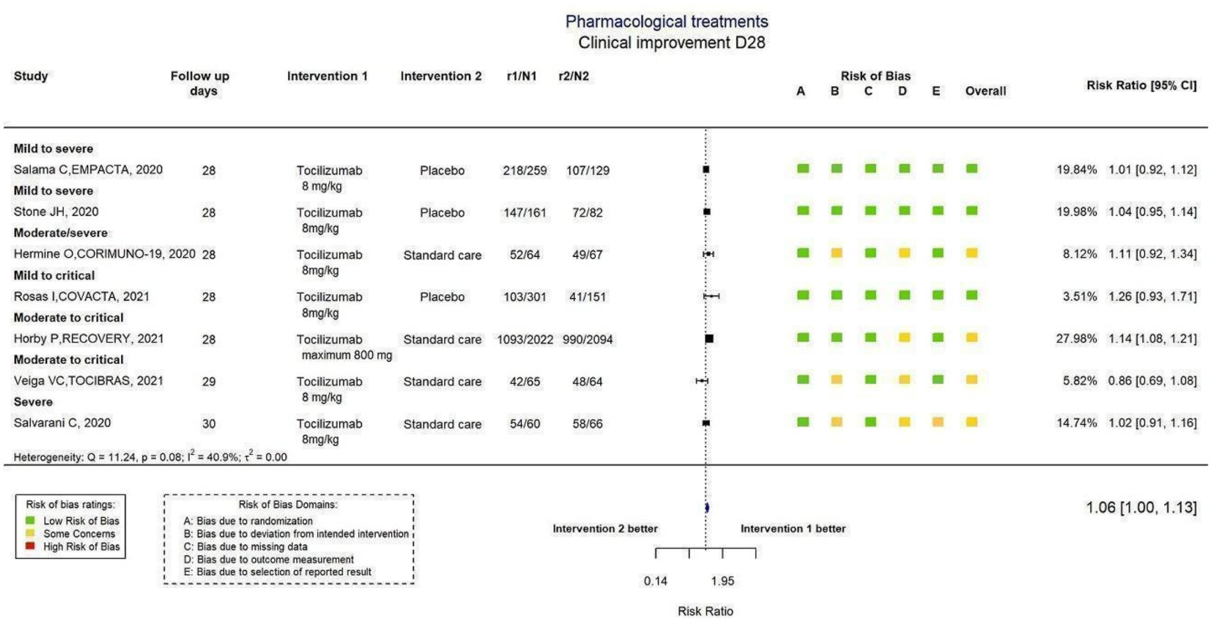

***Figure 2**. Forest plot showing clinical improvement D28 on tocilizumab compared to standard of care/placebo* [7]

Severe COVID-19 patients admitted in the ICU were randomized within 24 hours of starting oxygen support to tocilizumab (n=353), sarilumab (n=48) or standard of care alone. Glucocorticoids were given at the start of enrolment or within the following 48 hours to 93% (610/654) of the patients. There were more organ support-free days for those given tocilizumab (OR 1.64, 95% CI 1.25 to 2.14) and sarilumab (1.76, 95% 1.17 to 2.91) compared to standard of care alone. The in-hospital survival for tocilizumab (OR 1.64, 95% CI 1.14 to 2.35) and sarilumab (OR 2.01, 95% CI 1.18 to 4.71) were likewise better compared to standard of care alone.[8]

The effect of sarilumab compared to standard of care/placebo on all-cause mortality at day 28 (RR 0.77, 95% CI 0.43 to 1.36) and on all-cause mortality at ≥ D60 (RR 1.00, 95% CI 0.50 to 2.0) for moderate to severe COVID-19 is uncertain.[7] In a multinational double-blind, placebo-controlled, Phase 3 randomized trial in hospitalized patients with severe to critical COVID-19 (n=416), sarilumab did not show any difference in time to clinical improvement compared to placebo [10 days for sarilumab 200 mg (HR 1.03, 95% CI 0.75–1.40) and 10 days for sarilumab 400 mg (HR 1.14, 95% CI 0.84–1.54) vs 12 days for placebo].[16]

A single-center case-control study on the use of siltuximab in adult COVID-19 patients with ARDS has been completed (NCT04322188). Interim data showed reduced need for ventilation for most of the included patients.[17]

The National Institutes of Health COVID-19 Treatment Guideline Panel and Consensus Panel of Philippine COVID-19 Living Recommendations recommend the use of tocilizumab as addition to dexamethasone/glucocorticoid among recently hospitalized COVID-19 patients who are on high-flow oxygen or greater support and have either been admitted to the ICU within the prior 24 hours or have significantly elevated inflammatory markers.[15, 18] The Infectious Diseases Society of America (IDSA) and the National Health Service in the United Kingdom likewise have the same recommendations for the same group of patients.[19,20]

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[21]
   - 4-8 mg/kg single dose or 400 mg 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[22]

   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[23]

B. Sarilumab: 400 mg single IV dose or 200-400 mg SC dose[24]

C. Siltuximab: 11 mg/kg infused over one hour with a potential second dose at the physician's discretion[17]

Adverse Effects

The adverse events reported in the clinical trials among those given tocilizumab were secondary bacterial infection, bleeding events, increased alanine aminotransferase level, decreased neutrophil count, and cardiac events.[8,10,13]

Both tocilizumab and sarilumab carry FDA black box warnings of serious infections, such as tuberculosis and invasive fungal infections, leading to hospitalization or death.

Tocilizumab should be avoided in patients with the following conditions: with known hypersensitivity to the drug, significantly immunocompromised, with alanine transferase >5 times the upper limit of normal, with uncontrolled serious bacterial, fungal, or non-SARSCoV2 viral infection, absolute neutrophil count <500 cells/μL, or with platelet count <50,000 cells/μL.[18]

Conclusion

Large RCTs showed benefit in terms of reducing mortality with tocilizumab, when used with a corticosteroid, among COVID-19 patients who are on high-flow oxygen or more intensive respiratory support and that had either been admitted to the ICU within the prior 24 hours or had significantly elevated inflammatory markers.

The use of sarilumab for severe to critical COVID-19 is uncertain. The findings of ongoing trials on sarilumab may establish the efficacy and safety for moderate to severe COVID-19.

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4. BRUTON'S TYROSINE KINASE (BTK) INHIBITORS

Mary Anne Roldan Castor, MD

Introduction

Bruton tyrosine kinase (BTK) is an enzyme involved in the synthesis of several inflammatory cytokines. It is a key player in B-cell antigen receptor (BCR) signaling that regulates B-cell growth. It also participates in signal transduction through growth-factor receptors, Toll-like receptors, integrins and G-protein-coupled receptors.[1]

Mechanism of Action

BTK inhibitors binds covalently to BTK and have broad immunosuppressive effects. They prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation. They are currently used for the treatment of B-cell malignancies and chronic graft-versus-host disease in stem cell transplant recipients.[2] Ibrutinib, a first generation BTK inhibitor, has been approved by US FDA for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, marginal zone lymphoma and chronic graft-versus-host disease in allogeneic stem cell transplantation.[3] It has been reported to cause cytopenias, infection, pneumonitis, diarrhea, bleeding, and atrial fibrillation. Acalabrutinib is a second-generation, oral BTK inhibitor which has less toxicity compared to its first-generation counterparts.[4] Zanubrutinib is also a second-generation oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[2]

Clinical Studies

Acalabrutinib

A small prospective study that included 19 hospitalized patients with severe COVID-19 given acalabrutinib, a BTK inhibitor, showed that among patients in the supplemental oxygen cohort, 73% no longer required supplemental oxygen and had been discharged from the hospital. Among those on invasive mechanical ventilation, 50% were extubated. These results need confirmation in a randomized, double-blind, placebo-controlled trial.[5]

The CALAVI Phase II trials (randomized, open-label, multicenter) for Calquence (acalabrutinib) in patients hospitalized with respiratory symptoms of COVID-19 did not meet the primary efficacy endpoint (respiratory failure or death).[6]

Zanubrutinib

A Phase 2 clinical trial which looked into the use of oral zanubrutinib compared to placebo among patients hospitalized for respiratory symptoms of COVID-19 and requiring supplemental oxygen without mechanical ventilation showed that it did not meet the primary efficacy endpoints of respiratory failure-free survival or reduction in days on oxygen. There were no new or additional safety signals identified in the trial.[7]

Ibrutinib

A retrospective case series involving 6 patients on Ibrutinib for Waldenstrom macroglobulinemia who had COVID-19 showed that 5 of the 6 who had ibrutinib at 420 mg/day did not experience dyspnea and did not require hospitalization. One patient was on low dose ibrutinib (140 mg/day) because of arthralgia. He had progressive dyspnea and hypoxia necessitating hospitalization. On hospitalization, ibrutinib was discontinued with worsening of the hypoxia. Ibrutinib was restarted at the same low dose, with tocilizumab and IVIG, on his 5th hospital day with improvement in oxygenation; but on his 10th hospital day he had worsening hypoxia. Ibrutinib was increased to 420 mg/day, given the mild course of the other 5 patients, with subsequent improvement.[8] This was also what happened with an 81-year-old patient with Waldenstrom macroglobulinemia. Ibrutinib was discontinued because it might cause further immunosuppression, but he developed increasing oxygen requirement and was admitted to the ICU. When ibrutinib was resumed with remdesivir; his oxygen requirement decreased in less than 24 hours.[9] A 77-year-old patient with chronic lymphocytic leukemia also had discontinuation of ibrutinib and was placed on mechanical ventilation. He was extubated 9 days after ibrutinib was resumed with hydroxychloroquine and 2 doses of tocilizumab.[10]

The National Institutes of Health COVID-19 Treatment Guidelines Panel recommends against the use of Bruton's tyrosine kinase (BTK) inhibitors, such as acalabrutinib, ibrutinib, and zanubrutinib for the treatment of COVID-19, except in a clinical trial. There are 5 clinical trials registered in ClinicalTrials.gov for acalabrutinib (with 3 completed and 1 terminated)[11], 1 for zanubrutinib[12], and 3 for ibrutinib[13].

Recommended Dose

Acalabrutinib:	100 mg orally or per enteric feeding tube twice daily for 10 days[5]
Zanubrutinib:	160 mg BID PO or 320 mg / day PO until disease progression or unacceptable toxicity[14]
Ibrutinib:	420 mg / day[7]

Adverse Effects

The most common adverse events of acalabrutinib were headache and diarrhea, but no patients discontinued treatment because of them.[16]

Adverse events for zanubrutinib include febrile neutropenia, thrombocytopenia, neutropenia, thrombocytopenia with significant bleeding, and non-hematologic toxicities.[14]

Ibrutinib adverse effects include cutaneous side effects (petechiae, bruising, palpable purpuric rash), hair and nail toxicities (brittle fingernails and splitting), hematologic complications (bleeding, cytopenias), cardiac side effects (atrial fibrillation, sudden cardiac deaths and ventricular arrhythmias), hypertension, infections, and diarrhea.[3]

Conclusion

There are very few published studies on the use of Bruton tyrosine kinase inhibitors. It should only be used in the context of a clinical trial.

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5. IVERMECTIN

Maria Carmela A. Kasala MD, Pauline Florence R. Santos Estrella MD, Mary Grace V. Toledo MD

Introduction

Ivermectin is a semi-synthetic derivative of avermectin, a macrocyclic lactone from the soil microorganism Streptomyces avermitilis. After its discovery and development, it was introduced into the animal health market successfully. Following that success, the drug was further tested to conquer filarial disease in humans[1]. Currently, it is a medication that is licensed and approved as an antiparasitic and an antihelminthic, used to treat several neglected diseases such as onchocerciasis, helminthiasis and scabies[2]. In vitro, it has been found to have a broad-spectrum antiviral activity[3]. Recently, numerous clinical trials have sought to repurpose Ivermectin for the prevention and treatment of COVID-19[4].

Mechanism of Action

Ivermectin, in vitro, is an inhibitor of the causative virus SARS-CoV-2. The proposed antiviral action on the corona virus is that Ivermectin binds into Importin alpha/Beta 1 heterodimer nuclear transport proteins which the virus uses as the transport to enter the cell's nucleus. Ivermectin binds to and destabilizes the Imp a/B1 heterodimer thereby preventing Imp a/B1 from binding to the viral protein and preventing it from entering the nucleus, resulting in a more efficient antiviral response[5,6].

Additionally, it is postulated to interfere with the attachment of the SARS-CoV-2 spike protein to the human cell membrane ACE-2 receptors[7]. Some animal studies have reported of Ivermectin having potential anti-inflammatory properties that suppress cytokine storms which may cause leakage of fluids into the alveolar spaces in the lungs, blocking O2 intake, multisystem organ failure and eventually, death[8]. However, in humans the concentrations needed for in vitro inhibition are unlikely to be achieved by the doses proposed for COVID-19 [9,10,11].

Clinical Studies

Several randomized clinical trials and retrospective cohort studies of Ivermectin use in COVID-19 all over the world have been reviewed by respected scientific advisory groups.

The National Institute of Health (NIH), a medical research agency in the United States, listed 11 key studies of various degrees of severity, 6 of which are randomized control trials, 2 open label and 3 retrospective studies. These included 1,027 participants for the clinical trials and 6,207 for the retrospective studies. Among the studies, 5 were published and 6 were preprints and not peer-reviewed. Some of the clinical studies revealed no benefits or worsening of disease, some reported shorter time to resolution of disease manifestations and shorter time to viral clearance or lower mortality rates. However, the trials were of small sample sizes and were done with concomitant medications such as Doxycycline, Hydroxychloroquine, Azithromycin, Vitamin C, Zinc, Vitamin D3 and Dexamethasone, making it difficult to ascertain the efficacy and safety of the use of Ivermectin alone for treatment of COVID 19. As of February 11, 2021, the National Institute of Health states that there are insufficient data to recommend either for or against the use of Ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of Ivermectin in the treatment of COVID-19[12].

The Living WHO guidelines review on Ivermectin for COVID-19 was based on a review of 16 trials with 2,407 participants, 75% of which examined patients with non-severe disease and 25% with both severe and non-severe patients. A few of those trials did not report any outcomes of interest. Of the trials, 25% were published in peer-reviewed journals, 44% as preprints and 31% were completed but unpublished. The effects of Ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance are unclear because of very low certainty of evidence. Despite point estimates appearing to show benefit of the use of Ivermectin for COVID-19, imprecision of aggregate data due to wide confidence intervals and small samples sizes plus high risk of bias due to inadequate blinding and randomization of patients lower data quality to make definite conclusions. (Figure 1) As of March 31, 2021, the Living WHO guidelines recommends NOT to use Ivermectin in patients with COVID-19 of any disease severity, except in the context of a clinical trial, because of few RCTs with low degree of certainty of evidence. The evidence also suggested possible harm associated with treatment, with increased adverse events.[13]

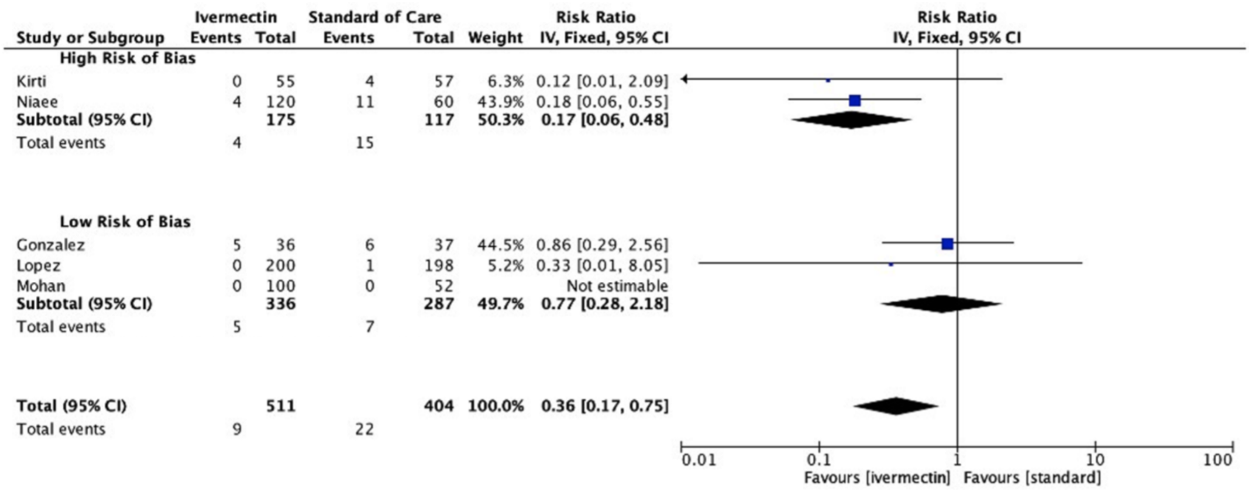

Figure 1. *Forest plot demonstrating direct comparison of ivermectin versus standard of care for mortality with subgroup analysis by risk of bias (from the Guideline Therapeutics and COVID-19: living guideline)*

The European Medicines Agency (EMA) also reviewed the latest evidence on the use of Ivermectin for the prevention and treatment of COVID-19. Results from clinical studies were varied, with some studies showing no benefit and others reporting a potential benefit. Most studies EMA reviewed were small and had additional limitations, including different dosing regimens and use of concomitant medications. EMA concluded that the available data do not support its use for COVID-19 outside well-designed clinical trials[14].

As of April 27, 2021, in the Philippine COVID-19 Living Guidelines, the Institute of Clinical Epidemiology, National Institute of Health, UP Manila in cooperation with the Philippine Society for Microbiology and Infectious Diseases states that there is insufficient evidence to recommend the use of Ivermectin in the treatment of patients with mild to moderate COVID-19. They suggest against the use of Ivermectin for the treatment of patients with severe COVID-19[15].

Recently, Ivermectin has been promoted by certain groups, including the British Ivermectin Recommendation Development (BIRD) panel, a private medical research company composed of health professionals, COVID-19 patients and other public members, based in Bath, United Kingdom. They reviewed 19 clinical trials involving 2,165 participants, for the treatment of COVID-19. Most trials included patients who had mild to moderate COVID-19, while 4 trials were on severely ill patients. The following outcomes were looked into: death, admission to ICU, need for mechanical ventilation, recovery (negative PCR), clinical recovery, length of hospital stay, improvement, deterioration, admission to hospital, severe adverse events. As of February 20, 2021, the British Ivermectin Recommendation Development (BIRD) panel recommends Ivermectin for the prevention and treatment of COVID-19 to reduce morbidity and mortality associated with COVID-19 infection and to prevent COVID-19 infection among those at higher risk[16]. However, 11 clinical trials were preprints and were not peer-reviewed. Of the remaining completed and published clinical trials, 5 had low risk of bias, the others had moderate to high risk of bias. Most of the evidence were of very low to low certainty. Confounding factors such as high risk of bias, small sample size, varying dosages and use of concomitant medications also do not allow for concrete recommendations to be made.

Recommended Dose

A wide range of dosing and schedules of Ivermectin were evaluated in the different published clinical trials involving patients of various degrees of severity of COVID-19.

Study	Dose	Severity of Covid Disease in Patients
Ahmed et al. [17]	12 mg per day for 5 days	Mild
Chachar et al.[18]	12 mg initial dose followed by 12 mg after 12 and 24 hours	Mild
Lopez-Medina et al.[19]	300 μg/kg per day for 5 days	Mild
Chaccour et al.[20]	400 μg/kg single dose	Mild
Chowdhury et al.[21]	200 μg/kg single dose + Doxycycline 100mg twice daily for 10 days	Mild
Mourya et al.[22]	12 mg once a day for 7 days + Hydroxychloroquine 400 mg twice daily + Azithromycin 500 mg once a day	Mild
Kishoria et al.[23]	12 mg single dose + Hydroxychloroquine 400 mg twice daily + Vitamin C 1 tab twice daily	Mild
Pott-Junior et al.[24]	dose varies in three arms 100, 200, 400μg/kg	Mild
Podder et al.[25]	200 μg/kg single dose	Mild/Moderate
Babalola et al.[26]	6 mg Ivermectin every 84hrs 2x a week or 12mg every 84 hrs. x 2 weeks	Mild/Moderate
Spoorthi et al.[27]	200 μg/kg single dose + Doxycycline 100 mg twice daily x 7 days	Mild/Moderate
Elalfy et al.[28]	200 - 400 μg/kg days 1, 4, 7, 10, 13 + Nitazoxanide 500 mg + Ribavirin 1200 mg + Zinc 30 mg BID	Mild/Moderate
Galan et al.[29]	14 mg per day for 3 days	Severe
Okumus et al.[30]	0.2 mg/kg x 5 days	Severe
Camprubi et al.[31]	200 μg/kg single dose + Hydroxychloroquine + Azithromycin	Severe
Rajter et al.[32]	200 μg/kg single dose + Hydroxychloroquine + Azithromycin	Severe

Adverse Events

The product label for Ivermectin notes the common side effects of headache, dizziness, muscle pain, nausea, diarrhea, swelling of hands / ankles / feet, swelling or tenderness of lymph nodes, itching and skin rash. The most common adverse events mentioned in the clinical trials were GI disturbances[27,28] such as abdominal pain[24], heartburn[18]. Other adverse events were headache[18], dizziness[20,24] muscle pain[24], blurring of vision[20] colored urine and palpitation[28].

The neurological side effects that were mentioned in the studies were confusion[20], agitation, delirium-like behavior, aggressive attitude, altered state of consciousness[30]. These were almost similar to the reported neurological adverse events in a case series such as difficulty in walking, disturbed or depressed and even loss of consciousness, seizures, coma and tremor. These events occurred without reports of overdosing but in doses ranging from 3-24 mg. Deaths have also been reported with one autopsy showing increased Ivermectin levels in the brain 14 days after the last dose.[33]

Conclusion

While antiviral activity of Ivermectin in vitro against SARS-CoV-2 has been discovered, careful risk–benefit analysis must be considered in real life, especially in critically ill patients. Furthermore, concerns of neurotoxicity with high dose use are present. Most of the completed studies on Ivermectin for COVID-19 have methodological concerns and with confounding variables. It would be worthwhile to await the results of ongoing clinical trials before recommending the use of Ivermectin for COVID-19.

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6. TRADITIONAL CHINESE MEDICINE: LIANHUA QINGWEN (LHQW)

Katrina Faith A. San Gabriel, MD

Introduction

Lianhua Qingwen Formula (LQF) is a traditional herbal prescription commonly used in China for the treatment and prevention of viral influenza prior to the COVID 19 pandemic. LQF contains 13 ingredients including Radix isatidis (isatidis root), Fructus forsythiae (forsythia), Lonicerae japonicae (honeysuckle), Rhizoma dryopteridis crassirhizomatis (basket fern), Herba ephedrae (mahuang), Semen armeniacae amarum (bitter apricot seed), Herba houttuyniae (yuxingcao), Herba pogostemonis (agastache), Radix et rhizoma rhodiolae crenulatae (rhodiola), Radix et rhizoma Rhei (dahuang) and Radix et rhizoma Glycyrrhizae (licorice), Gypsum fibrosum mineral (shigao) and menthol.[1]

Mechanisms of Action

There are 15 pharmacologically significant components (arctiin, emodin, formononetin, forsythoside A, gallic acid, hesperidin, isoliquiritigenin, kaempferol, ononin, phillyrin, quercetin, rutin, salidroside, secoxyloganin and tricin) identified in LQF.[1] Arctiin is anti-inflammatory, anti-microbial and proven to be therapeutic against influenza by blocking hydrogen peroxide-induced senescence and cell death. Formononetin is a plant-derived phytoestrogen reported to activate the T-cell cytoplasmic 1 signaling pathway and increase the expression and secretion of T cells. Gallic acid and hesperidin both have anti-inflammatory and antioxidant effects. Isoliquiritigenin has been proven as a potent inhibitor of inflammasome activation.[2] Kaempferol exhibits high activity against two types of influenza viruses, H1N1 and H9N2.[3] Phillyrin is the main chemical constituent of forsythia and has been reported to attenuate pulmonary inflammation.[4] Quercetin and rutin both exhibit anti-H5N1 viral and antioxidant activity.[5]

In vitro, LHQW capsules inhibit the proliferation of influenza viruses of various strain with the 50 % inhibitory concentration ranging from 0.35 to 2 mg/mL. It blocks the early stages (0−2 h) of virus infection, and reduces virus-induced nuclear factor-kappa B (NF-κB) activation and the gene expression of interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α, interferon-inducible protein (IP)-10, and monocyte chemoattractant protein (MCP)-1.[6]

Multiple studies have used network pharmacology and molecular docking analyses on Lianhua Qingwen (LHQW) Capsule to elucidate the potential mechanisms of the drug in the treatment of COVID-19. Gene Ontology and KEGG analyses indicate that LHQW can act by regulating immune response, apoptosis and virus infection. PPI network and subnetworks identified the most significant gene Akt1, which is involved in lung injury, lung fibrogenesis and virus infection. Six active compounds of LHQW can enter the active pocket of Akt1 and can potentially regulate Akt1 gene activity.[7] The main active ingredients of LHQW were also verified by molecular docking with angiotensin-converting enzyme 2 (ACE2), another potential therapeutic target for COVID-19.[8]

Clinical Studies and Trials

A systematic review and meta-analysis published March 2021, evaluated the efficacy and safety of LQC in the treatment of patients with COVID-19. Three RCTs, three case control studies and 2 case series from a literature search through six databases (China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang database, PubMed, Embase, and Web of Science (WoS)) were included with a total sample size of 924 patients with mild to moderate disease. The study concluded that LHQW combined with conventional treatment (e.g. oxygen therapy, antiviral, antimicrobial) had a higher overall efficacy rate (RR = 1.16, 95% CI : 1.04∼1.30, P = 0.01) and CT recovery rate (RR=1.21, 95% CIs: 1.02∼1.43, P = 0.03). However, the authors disclose certain limitations such as the small sample size and that all studies were done in China which may not fully reflect the global situation and should be interpreted with caution. Although the characteristics of the patients included in the study did not differ significantly, some factors (such as comorbidities) were not evaluated and may affect the accuracy of the results. There was also a lack of data for subgroup analysis and the data for meta-analysis was only limited to two randomized controlled trials.[9]

A prospective multicenter randomized controlled trial in confirmed COVID-19 cases by Hu et al on 284 patients (142 each in treatment and control group), showed that the usual treatment (oxygen therapy, antiviral medications and symptomatic therapies) in combination with LHQW capsules (4 capsules thrice daily for 14 days) had significantly higher recovery rate and shorter median time to symptom recovery (fever, fatigue, and coughing), as compared with control group. However, both groups did not differ in the rate of conversion to severe cases or viral assay findings.[10]

Yu et al. published a clinical study on the treatment of mild COVID-19 with LHQW granules (6 g, tid) combined with umifenovir (0.2 g, TID). Their findings showed that the efficacy of LHQW granules combined with umifenovir (LHQW group) was significantly higher than that of the umifenovir group (80.95 % vs 64.86 %), while the rate of severe illness was markedly lower (14.29 % vs 23.65 %). After 7 days of treatment, the main TCM syndrome scores (fever, fatigue, cough, dry throat, chest tightness), C-reactive protein and procalcitonin levels in the LHQW group were significantly lower, and the white blood cell and lymphocyte counts were obviously higher than those in the umifenovir group. [11]

Recommended Dose

The recommended dose for LHQW is (350 mg/capsule) 3 to 4 capsules 3 x a day (3 grams to 4 grams a day).

Adverse Effects

Lianhua qingwen contains mahuang which is an herb from which ephedrine is extracted, and this may cause nausea, vomiting, abdominal pain, diarrhea, rashes, itching, dry mouth and dizziness.

In the study by Liu et al, there was a higher incidence of abnormal liver function in the LQC group.[12] People with pre-existing liver, thyroid and heart disease (including hypertension and arrhythmias) should take LQC with caution and only with the approval of their attending physician.

Conclusion

Lianhua Qingwen may have beneficial effects in the treatment of patients with COVID-19. However, with the lack of good quality studies and randomized controlled trials currently available in literature, more studies are needed to verify its effectiveness, efficacy and safety.

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OTHER IMMUNOMODULATORS USED IN COVID-19

PATHOGEN-SPECIFIC IMMUNOMODULATORS

1. INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Mary Anne R. Castor, MD, Marysia T. Recto, MD, Lara Theresa A. Aleta, MD,
Cherie O. Cervantes, MD, Ma. Socorro A. De Jesus, MD, Jenifer O. Agustin, MD,
Alric V. Mondragon, MD, Roxanne C. Hao, MD, Aimee Lou M. Nano, MD

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]

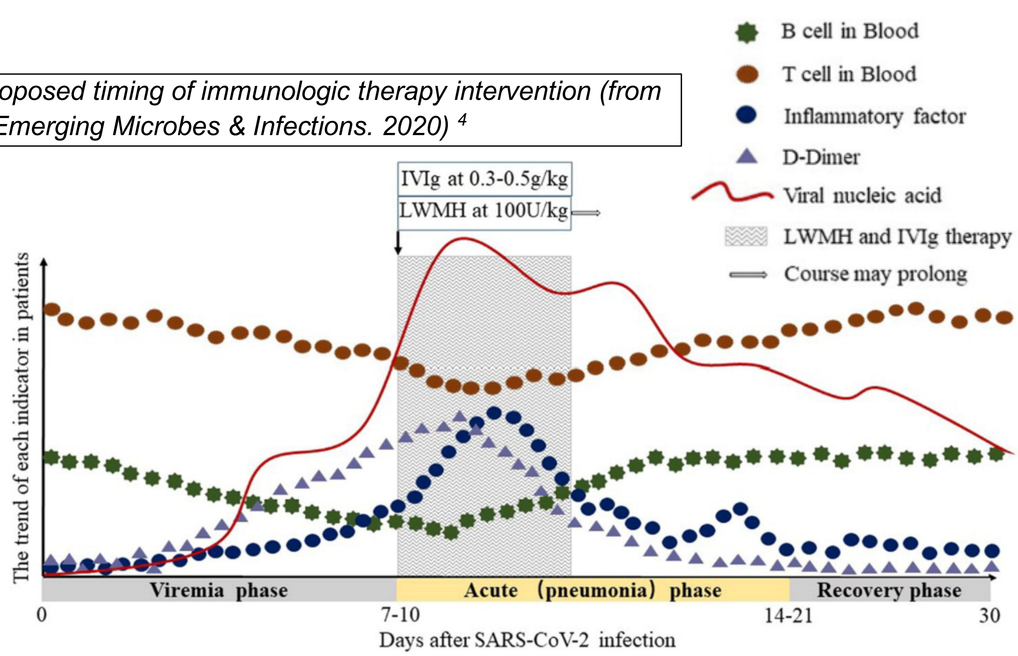
Mechanism of action and effect on COVID-19 infection

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 1)[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 1**. Proposed timing of immunologic therapy intervention (from Lin L, et al. Emerging Microbes & Infections. 2020)* [4]



Efficacy Studies of IVIG in COVID-19 Infections

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 (*P*=0.872 and *P*=0.222, respectively). Sixty-day mortality was reduced by using IVIG in the early stage (≤7 days from admission) (*P*=0.008).[11] Another retrospective study showed that the ≤48 h group compared to the >48 h group had significantly shorter length of stay in the hospital (11.50 ± 1.030 vs 16.96 ± 1.620 days, *P*=0.0055), significantly lower proportion of patients requiring mechanical ventilation (6.67% vs 32.14%, *P*=0.016), and significantly longer 28-day survival time (*P*=0.0215).[12] A prospective cohort study by Zhou et al. involving 10 COVID-19 patients showed improvement in [APACHE score (9.10±6.15 vs 5.50±9.01, P<0.05), body temperature (37.59±1.16 vs 36.46±0.25, P<0.05), lymphocyte count (0.59±0.18 vs 1.36±0.51, P<0.05), lactate dehydrogenase (419.24±251.31 vs 257.40±177.88, P<0.05), and C-reactive protein (49.94±26.21 vs 14.58±15.25, P<0.05)] after giving moderate-dose corticosteroid and IVIG treatment.[13]

Presently, there are a few completed clinical trials investigating the efficacy of intravenous immunoglobulin therapy on COVID-19 patients. In a prospective randomized open label study, IVIG plus methylprednisolone was compared with standard of care treatment alone in the management of hospitalized COVID-19 patients. The results of this study showed that the IVIG plus methylprednisolone group, compared to the control group, has a shorter hospital stay (11 vs 19 d, *p* = 0.01 Mann Whitney *U* test), shorter ICU stay (2.5 vs 12.5 d, *p* = 0.006 Mann Whitey *U* test), and lower rate of progression to use of mechanical ventilation (2/14 vs 7/12, *p* = 0.038 Fisher exact test). The treatment group also showed greater improvement in Pao2/Fio2 at 7days (median [range] change from time of enrollment +131 [+35 to+330] vs +44·5 [–115 to +157], *p* = 0.01, Mann Whitney *U* test) than the control group. Results, however, may be confounded by co-intervention with methylprednisolone. The sample size was also small (n=34). A larger phase 3 randomized, double-blind trial is currently underway.[14]

In a randomized, double blind, placebo-controlled trial by Gharebaghi, et al on severe COVID-19 patients, one group was given immunoglobulin while the other group was given placebo. Results showed a significantly lower in-hospital mortality rate for the IVIG group compared to the placebo group (6 [20.0%] vs. 14 [48.3%], respectively; P = 0.022). However, this study served as a pilot study, with a small sample size (n=59).[15]

Raman, et al were able to demonstrate in an open label, multi-center, randomized study on COVID-19 patients with moderate pneumonia that initiation of IVIG, as adjuvant treatment compared to standard of care alone, can significantly reduce the number of days to clinical improvement (7.7 days vs 17.5 days, P=0.0001). Clinical parameters, which include mean duration required to reduce the body temperature to<37°C, normalization of oxygen, mean duration for cessation of cough, and mean duration of mechanical ventilation showed significant improvement in the treatment group compared to the control group (P=0.005). They also noted that IVIG increased the proportion of patients with negative RT-PCR result on day 14 of illness. Mean duration in normalization of respiratory rate and number of days of stay in ICU did not show significant results.[16]

Another randomized controlled trial was done investigating the efficacy of IVIG by comparing IVIG plus hydroxychloroquine and lopinavir/ritonavir versus hydroxychloroquine and lopinavir/ritonavir as control in the treatment of severe COVID-19. Results show that there was no significant difference between the two groups in terms of mortality rate (P-value=0.8) and the need for mechanical ventilation (P-value=0.39). However, the study showed that the time between admission and IVIG initiation and the length of stay in the hospital and ICU are positively correlated, hinting that early IVIG initiation may be beneficial.[17]

There are systematic reviews with meta-analyses done on studies on the various treatments currently being used in the management of COVID 19 patients. Only a few clinical trials on IVIG were included in these reviews.

In The LIVING Project, a living systematic review, two randomized clinical trials on IVIG were included. Meta-analysis showed a beneficial effect of intravenous immunoglobulin versus control on all-cause mortality (RR 0.40; 95% CI 0.19 to 0.87; *p* = 0.02) (Figure 2). However, these trials were evaluated to be at high risk of bias and that there is very low certainty evidence (GRADE) that IVIG might reduce the risk of death.[18]

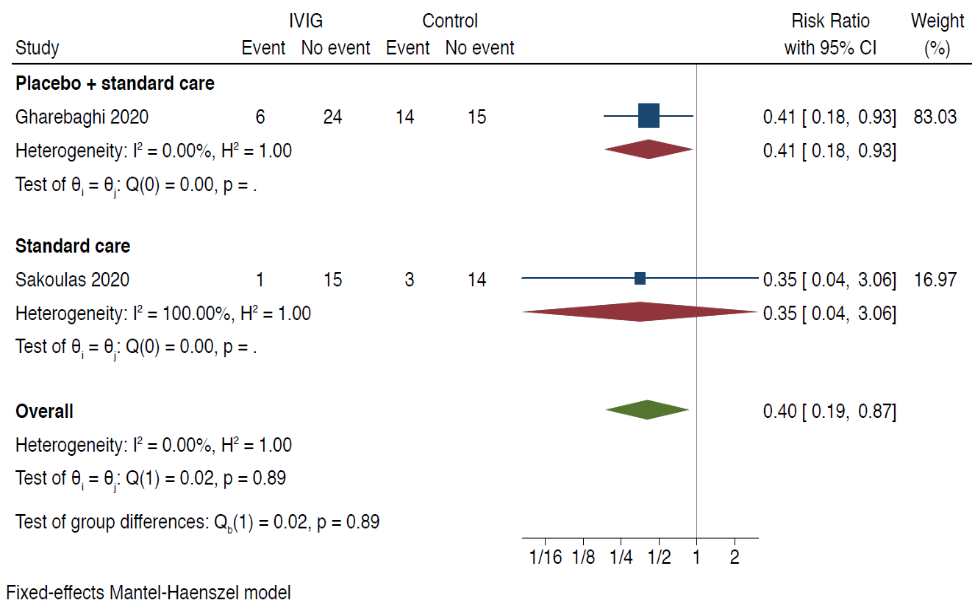


Figure 2. *Trial sequential analysis of intravenous immunoglobin versus control interventions (standard care or placebo) on all-cause mortality (From Juul S., et al)* [18]

Likewise, Zhang et al did a review on various clinical trials on COVID-19 treatments. This showed that in terms of reducing mortality rate, IVIG might be of potential benefit compared to standard of care treatment for COVID-19, but with low certainty
(Figure 3).[19]

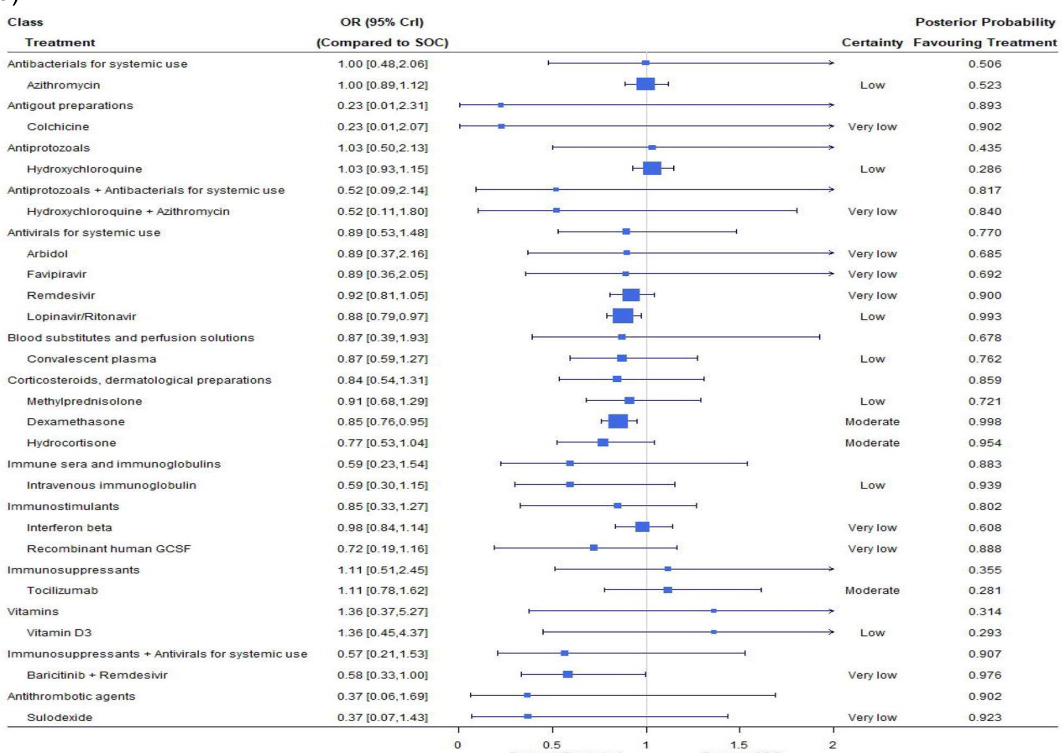


Figure 3. *Mortality under treatments compared with the standard of care (SOC); OR is the odds ratio and CrI represents credible interval (From Zhang C., et al)*[19]

The review done by Pei et al on the use of antivirals, corticosteroids, antibiotics, and IVIG for treatment of COVID 19 included six studies. Four of which are retrospective studies on IVIG. This review revealed that IVIG had a nonsignificant effect on mortality (OR, 2.66; 95% CI, 0.72–9.89; P = 0.14; $I2$ = 93.1%) (Figure 4).[20]

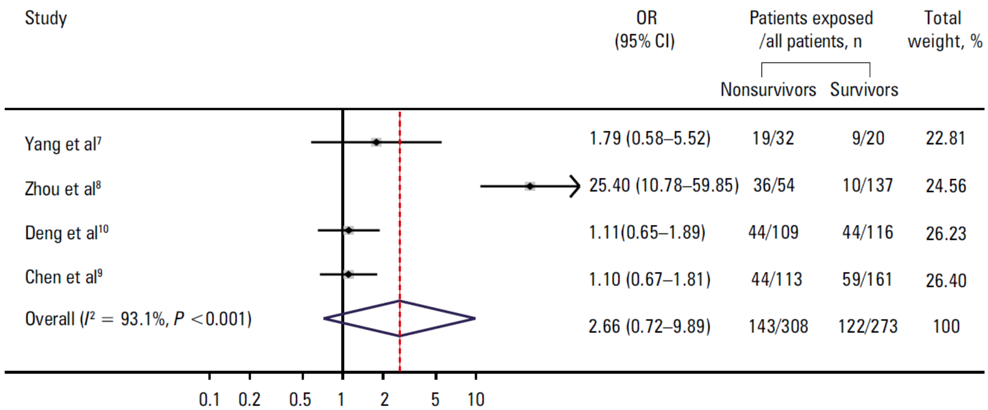


Figure 4. *Retrospective studies on the impact of IVIG use on mortality.*

Another review included an RCT and a retrospective study on IVIG. The review showed that high dose IVIG is associated with reduced mortality rate in critically ill COVID 19 patients (OR 0.13, 95% CI 0.03 to 0.49, p = 0.003) (Figure 5). However, they noted that their review has overall low level of evidence since it is based mostly on observational studies.[21]

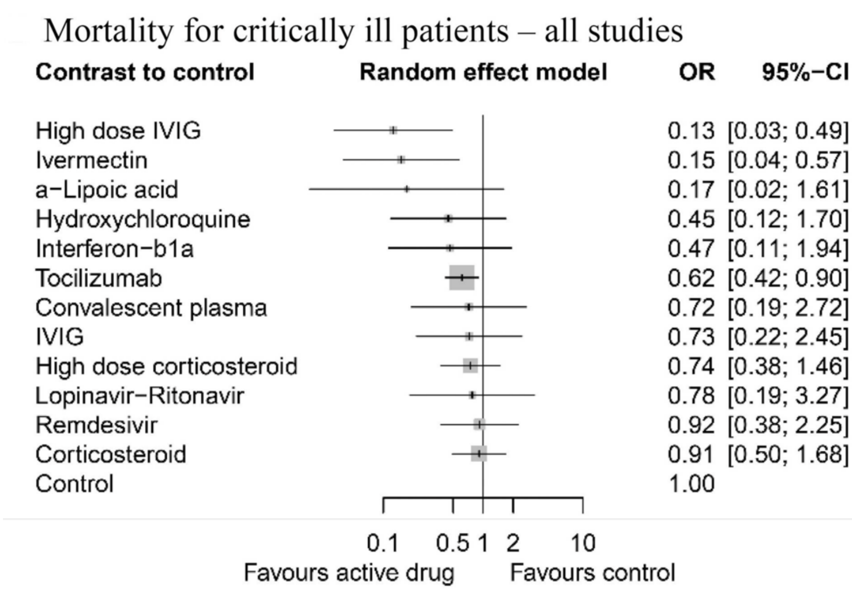


Figure 5. *Network meta-analysis of pharmacological interventions compared with control (standard care) for mortality for critically-ill patient*

More clinical trials with enough sample size are needed to establish the use of IVIG in the treatment of COVID 19. As of April 15, 2021, there are 12 clinical trials listed at clinicaltrials.gov. Four of which have already completed their studies and four are currently recruiting.

Recommendations of Governing Bodies

National Institutes of Health/Centers for Disease Control and Prevention

The COVID-19 Treatment Guidelines Panel recommends against the use of intravenous immunoglobulin (IVIG) for the treatment of COVID-19, except in a clinical trial (Strong, Expert Opinion). This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.[22]

Philippine Society for Microbiology and Infectious Diseases

There is insufficient evidence to support the use of intravenous immunoglobulin (IVIg) for the management of COVID-19 among severe hospitalized patients except in the context of a clinical trial.[23]

Philippine Pediatric Society

IVIG should not be routinely given for pediatric COVID-19. However, it can be given for patients presenting with a multisystem inflammatory syndrome, especially those with a Kawasaki disease-like presentation.[24]

Recommended 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.[25]
2. Suggested IVIG dose is: 0.3-0.5 g/kg/day for 3 to 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.[18-21, 25]

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.[26] 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.[27-28]

Conclusion

The use of IVIG may be beneficial when used early in the course of illness but more clinical trials with enough sample size are needed to establish the use of IVIG in the treatment of COVID 19. 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

Fatima Johanna T. Santos-Ocampo, MD, Aileen A. Elorde, MD, Maria Rowena B. Valerio, MD

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 4) seem to be consistent with some anti-inflammatory effects.

Clinical Studies

In this present epidemic caused by SARS-CoV-2, there were 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 and maintain the neutralizing antibodies at high levels leading to the disappearance of viremia in 7 days.[6]

The other 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]

With accumulation of data from clinical trials, a systematic review of convalescent plasma and hyper-immune globulin for patients with COVID-19 was published in July 2020 in the Cochrane Database.[8] In October 2020, a second update was published that included 19 studies [2 randomized controlled trials (RCTs), 8 controlled non-randomized studies on intervention (NRSIs), 9 non-controlled NRSIs] with a total of 38,160 participants, of whom 36,081 received convalescent plasma.[9] Results for all-cause mortality (NSRI RR 0.89, 95% CI 0.61-1.31), time to death (RCT HR 0.74, 95% CI 0.30-1.82; NRSI HR 0.46, 95%

CI 0.22-0.96), and improvement of clinical symptoms (at day 7 RCT RR 0.98, 95% CI 0.30-3.19) were mostly inconclusive with very low quality of evidence.[9]

A meta-analysis and systematic review by Janiaud et al. included 1060 patients from 4 peer reviewed RCTs, and 316 patients from 5 preprint RCTs, and 10406 patients from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial. It aimed to assess the clinical outcome with convalescent plasma vs placebo together with standard of care. It has incorporated the 2 RCT's previously analyzed in the living systematic review by Chai. et al. The overall result for the use of convalescent plasma with standard of care vs standard of care alone for all-cause mortality from the 10 RCTs was inconclusive (RR 1.02, 95% CI 0.92-1.12). Results were also inconclusive for length of hospital stay (RR 1.07, 95% CI 0.79-1.45) and need for mechanical ventilation (RR 0.81, 95% CI 0.42-1.58) (Figure 1). This meta-analysis included RCTs using convalescent plasma with high or low antibody titers, but no subgroup analysis was done. A titer of 1:640 or higher of S-protein receptor-binding domain–specific IgG antibody or 1:40 serum neutralization titer or higher was classified as high antibody titer. [10]

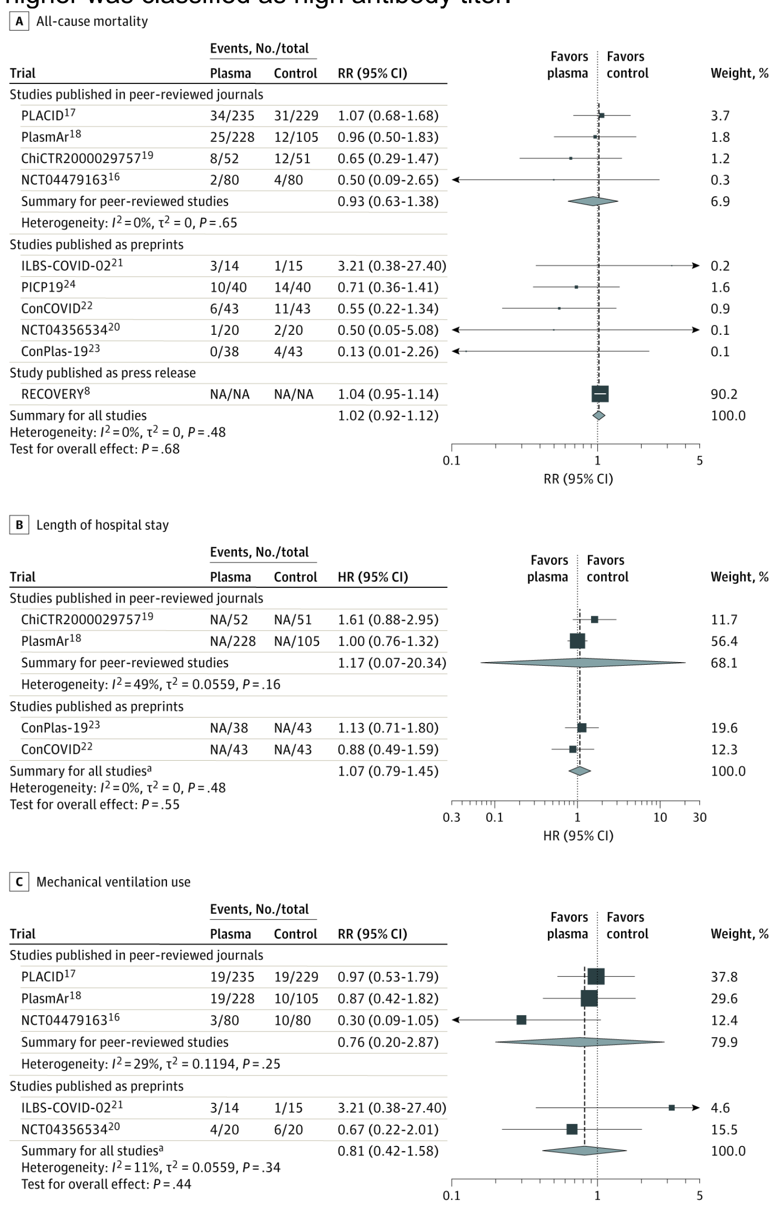

***Figure 1**. Association of Convalescent Plasma With All-Cause Mortality, Length of Hospital Stay, and Mechanical Ventilation Use in Peer-Reviewed Trials and Non–Peer-Reviewed Trials (Preprints and the RECOVERY Trial)[10]*

In the COVID-19 Living Data, result for all-cause mortality (RR 0.86, 95% CI 0.70-1.05) and clinical improvement at day 28 (RR 1.00, 95% CI 0.97-1.02) were also inconclusive.[11]

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 (8 to 10 ml/kg, with a maximum of 600 ml) once per day and up to three consecutive days has been suggested.[12,13,14]

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 to 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.[12] 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.[13]

Adverse Effects

There can be mild reactions like evanescent red spots as reported by Duan et al.[6] Other non-infectious hazards of transfusions are allergic transfusion reactions and transfusion associated circulatory overload (TACO).[12] The risk for these adverse effects are likely to be no different from those of standard plasma transfusion. However, it may carry some risk of transfusion related acute lung injury (TRALI)[15] 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.[16] 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.

For patients with impaired humoral immunity, SARS-CoV-2 viral replication may persist putting them at risk for developing viral resistance after treatment for SARS-CoV-2 with convalescent plasma.[17]

Conclusion

Evidence shows that improvement of survival or other clinical outcomes with the use of convalescent plasma is still inconclusive. The certainty of the evidence ranged from very low to moderate for all-cause mortality and low for other outcomes.

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3. HYPERIMMUNE GLOBULIN

Fatima Johanna T. Santos-Ocampo, MD

Introduction

Hyperimmune globulin is sourced from animal or human donors with high titers of the antibody of interest as determined by a particular standard[1]. It contains polyclonal antibodies, which can be used to treat viral infections[2]. They are concentrates of heterologous immunoglobulins, formed by intact IgG molecules or digested Fab, and F(ab′)2 fractions.[3,4] In the last fifteen years , several procedures for production of SARS-CoV hyperimmune globulin have been published . One entails pooling of convalescent plasma samples from different individuals with high antibody titers acquired via actual infection with the virus (natural immunity), prophylactic immunization or target immunization. Serum collected underwent cold ethanol precipitation. The separated serum portion of the blood was then subjected to ion-exchange chromatography followed by virus inactivation and removal procedures to ensure safety. Optimal titers of neutralizing antibodies were then achieved.[5]

An equine serum containing fractions of F(ab′)2 that produced a neutralizing effect for therapeutic use in SARS was also developed at around the same time.[6]
With this platform, the risk of serum sickness has drastically been reduced with the new generation of processed equine serum antibodies containing highly purified F(ab')2 fragments. With the removal of FC fragments, serum sickness and other adverse events became rare.[7] Examples of such products are included in the management of clinical emergencies, such as snakebite and scorpion sting envenomation, severe poisoning (tetanus toxin, digoxin and botulinum toxin) and severe infectious diseases .

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. Hyperimmune sera have been used to treat infections such as tetanus, diphtheria, rabies, SARS-CoV-1, MERS-CoV, Ebola and avian influenza virus safely and with effective results.[7]

Clinical Studies

At present, not enough evidence on actual COVID-19 patients can be cited as to the efficacy and safety of using hyperimmune globulin. Clinical trials are still ongoing.

Animal studies have begun with equine serum F (ab′) 2 against SARS-CoV-2 produced by the use of Receptor binding protein (RBD) as an immunogen, and its neutralizing power against SARS-CoV-2 was verified[8]. Cunha et al produced another type of anti-SARS-COV-2 equine serum derived from horses immunized with the trimeric spike glycoprotein of SARS-COV-2 and was likewise evaluated for antibody production.[9] This product generated an even greater immunogenic potency. The data obtained indicated that this particular production method produced neutralization titer up to 150 times that of convalescent plasma from 3 Brazilian donors thereby demonstrating the efficiency of the process. This and other similar studies can very well be a strong basis to embark on the next stages of pre-clinical, and clinical studies for COVID 19.[8]

Recommended Dose

No reference studies available.

Adverse Effects

Adverse effects if any is expected to be very similar to the adverse reactions of convalescent plasma preparations if given intravenously. Pending completion of clinical trials for equine derived hyperimmune globulin therapy and thorough analysis of ongoing trials (including the 138 tagged by the second update of the living systematic review from the Cochrane database which cited lack of completed trials on hyperimmune globulin), it is uncertain whether hyperimmune globulin therapy results in a clinically relevant increased risk of severe adverse reactions (SAEs).

Availability

The product is available only under study and clinical trial conditions.[10,11,12]

Conclusion

Hyperimmune globulin has potential for a more efficient cost/benefit approach to preventive therapy for COVID-19. Proof of its efficacy for prophylactic use will depend on the results of ongoing clinical trials. There are, however, no studies citing its use for treatment of moderate-severe COVID-19.

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NON-PATHOGEN-SPECIFIC IMMUNOMODULATORS

1. ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Beatrice S. Vicente Pascual, MD

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) (Figure 1). 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]

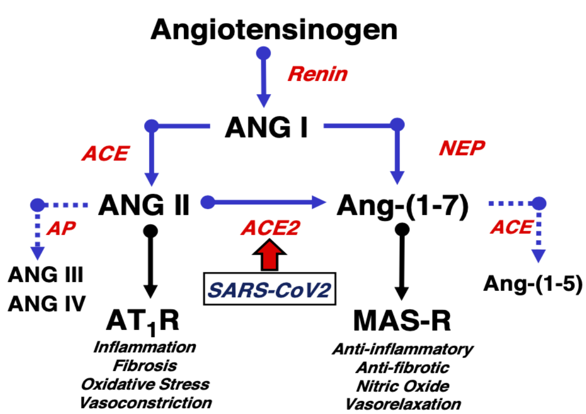

Figure 1. *Processing and Functional scheme of the Renin-Angiotensin system [4]*

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

According to the NIH COVID-19 Treatment Guidelines, patients with COVID-19 who are receiving **angiotensin-converting enzyme (ACE) inhibitors** or **angiotensin receptor blockers (ARBs)** for cardiovascular disease (or other non-COVID-19 indications) should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition.[12]

Furthermore, the COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **ACE inhibitors** or **ARBs** for the treatment of COVID-19, except in a clinical trial.[12]

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

Some of the common adverse effects of ACEI are cough, hyperkalemia, hypotension, kidney failure, pancreatitis, allergic reactions, angioedema.[9]

The ARBs on the other hand may cause hyperkalemia, cough, hypotension, dizziness, headache, drowsiness, metallic taste, kidney failure, liver failure and allergic reactions.[9]

Conclusion

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 as well as the National Institute of Health COVID-19 Treatment Guidelines have stated that (in patients with COVID-19) these agents should be maintained in those using them rather than withdrawing these drugs.[13,14]

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2. ALPHA 1 ADRENERGIC RECEPTOR ANTAGONISTS

Mary Anne Fran Cuaresma, MD

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 to 64 year old male patients who filled an α1-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 α1-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 α1-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]

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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3. AZATHIOPRINE

Ma. Fredelita C. Asuncion, MD

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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4. AZITHROMYCIN

Jennifer Serrano Flores, MD, Pascualito I. Concepcion, MD

Introduction

Azithromycin is a macrolide, belonging to a class of antimicrobials with activity mainly against gram-positive cocci and atypical pathogens.[1] It had a promising pharmacokinetic and pharmacological characteristics that could be useful in the treatment of SARS-CoV-2 infection.[2]

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[3] 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.[4]

Clinical Studies

At present, the CDC and NIH Treatment for COVID-19 recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients and non hospitalized patients, except in a clinical trial.[5] There was no mention about the use of Azithromycin alone in 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 of a previous cardiac pathology (arrhythmias, heart failure, hypokalemia, hypomagnesemia)[6,7,8] 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.[7,9]

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

Azithromycin should not be used routinely to treat COVID-19 in the community in the absence of additional indications. These findings have important antibiotic stewardship implications during this pandemic, as inappropriate use of antibiotics leads to increased antibiotic resistance.[10]

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5. BCG VACCINE

Rommel Crisenio M. Lobo, MD

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]

Currently, there are 15 clinical trials registered at ClinicalTrials.gov investigating the possible impact of BCG vaccine on COVID-19. Their primary outcome measure is the prevention of COVID-19 among vaccinated adults.

Conclusion

At this point in time, there is still no firm scientific evidence that supports the use of BCG vaccine in preventing and/or treating COVID-19 patients. Clinical trials are still underway.

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6. BETA-GLUCAN

Julia C. De Leon, MD

Introduction

β-glucans are naturally-occurring polysaccharides obtained from different sources such as oats, barley, bacteria, yeast, algae, and mushrooms. β-glucan derived from different sources have variation in their structure responsible for their specific biological properties.[1] There have been nearly 7,000 publications reporting the immune-modulating effects of β- glucans. Actions of β-glucan are not direct but rather due to β-glucan being a biological response modifier (BRM) to enhance immunity.

β-glucans are one of the main active components derived from mushrooms. There are some edible mushrooms with reported immunomodulatory actions. Lentinans are a specific class of β-glucans extracted from the edible mushroom *Lentinus edodes*, and are composed of a β-(1–3)-glucose backbone with two (1–6)-β-glucose branches of each five glucose units. There has been an increasing interest in their use for treating disease in animals and humans. McCarty and DiNicolantonio (2020) recently described the potential role of β-glucan as a natural nutraceutical for boosting type 1 interferon response to RNA viruses such as influenza and coronavirus.[3] Findings showed that β-glucan from shiitake mushrooms (*Lentinus edodes*) demonstrated potential for the treatment of lung injury, reducing IL-1β, IL-6 in an in vitro lung injury model, suggesting that it may ameliorate the cytokine storm that causes ARDS as seen in COVID-19.[4]

There is another specific β-glucan: a 1-3,1-6 β-glucan from a black yeast called *Aureobasidium pullulans* AFO-202 strain. It is a soluble β-glucan that contains both high and low molecular weight β-glucan. High molecular β-glucan (H-BG) has been found to stimulate the proliferation of lymphocytes with stronger effects and low molecular β-glucan (L-BG) component reduces the levels of inflammatory biomarkers (majorly cytokines), stimulates the cytokine and activates chemokine signaling pathways. This AFO-202 beta glucan decreases IL-6 levels. The increase in soluble Fas (sFas), which helps in regulating the immune response by immune suppression, will be highly valuable in regulating the cytokine storms and hyper-inflammation associated with COVID-19.[5]

Mechanism of Action

β-glucans are recognized by the immune system as a Pathogen Associated Molecular Patterns (PAMPs) which interact with Pathogen Recognition Receptors (PRRs) on innate immune cells, activating the immune response.

The most pronounced effect of β–glucans consists of augmentation of phagocytosis and proliferative activities of professional phagocytes-granulocytes, monocytes, macrophages and dendritic cells.[4] Here, macrophages are considered the basic effector cells in host defense versus bacteria, viruses, multicellular parasites, tumor cells and they play the most significant role.

When explored, β-glucan in one-way human mixed lymphocyte reaction (MLR) assay systems could activate suppressor cells—in particular, regulatory T cells (Treg)—and also induce the production of suppressive cytokines[5] which will be helpful in suppressing the cytokine storm observed in COVID-19. While the immunological actions of the AFO-202 β-glucan are evident and will have potential use against COVID-19 infection by immunosuppressing pro-inflammatory cytokines, several studies have also reported that this β-glucan can enhance immunity by increasing the levels of cytotoxic cells such as NK cells and macrophages, which will be the actual line of defense against the viruses.

Clinical Studies

As of August 10, 2020, there are no studies registered on the use of β-glucans for COVID-19. Human trials are needed to test for its efficacy against COVID-19.

Recommended Dose

The dose has not yet been established for COVID-19.

Adverse Effects

The potential harms of β-glucan in COVID-19 still needs further investigation, however, as a nutraceutical, few adverse effects have been described and yeast β–glucan has been given the generally regarded as safe (GRAS) status.[6,7]

Conclusion

The AFO-202 β-glucan has not yet been subjected to a clinical study in COVID-19 positive patients. The exact role in tackling COVID-19 has not been established.[8]

Further clinical studies are needed to refine β-glucan as a countermeasure for tackling cytokine storm that causes ARDS, as evident with COVID-19.[4]

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7. CALCINEURIN INHIBITORS

Maria Zoila G. Carandang, MD

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 (IL2) 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 the potential for viral suppression.

A. CYCLOSPORINE

Introduction

Cyclosporin-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 JRA, hematologic disorders and 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] There are a few articles have proposed that CINs may have a role in the treatment of COVID-19[1,9], and as of date 6 studies, in the recruiting stage, that propose to use Cyclosporine as intervention for COVID-19. There is one ongoing study, NCT04412785, specific for Cytokine Release Syndrome in Moderate COVID-19 patients. There are no current recommendations for the use of CIN from NIH, CDC or WHO.

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]

Conclusion

While there is a potential for use, there is limited evidence to evaluate the efficacy and safety of the Cyclosporine in patients with COVID-19.

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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 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.

There are no new trials involving Tacrolimus in the treatment of CRS in COVID19 patients.

Recommended Dose

Dose for COVID-19 therapy is still to be determined but the ongoing study suggests the dose necessary to obtain trough blood levels of 8-10 ng/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 Tacrolimus in patients with COVID-19.[9]

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8. COLCHICINE

Jenifer R. Otadoy-Agustin, MD

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

Of the 32 registered clinical trials involving colchicine in the treatment of COVID-19, four have been completed.

A study comparing colchicine with standard of care (SoC) (hydroxychloroquine, dexamethasone and/or lopinavir/ritonavir) showed a significantly higher survival rate (84.2% vs 63.6%) with colchicine among adult hospitalized patients with pneumonia and/or acute respiratory distress syndrome[7].

The GRECCO-19 Randomized Clinical Trial was a prospective, open-label study that included 105 patients in a 1:1 allocation to Colchicine in addition to SoC vs SoC alone. Patients on SoC alone had a higher clinical deterioration rate and a shorter time to clinical deterioration compared to those on colchicine & SoC[8].

A single center, randomized, double blind, placebo-controlled trial conducted in Brazil among hospitalized patients diagnosed with moderate to severe COVID-19 showed that treatment with colchicine and SoC (azithromycin, hydroxychloroquine, heparin, methylprednisolone) compared with SoC alone had a reduced need for supplemental oxygen therapy and a shorter hospital stay[9].

In a cross-sectional study of 301 patients presenting with severe covid pneumonia defined as alveolar pressure / inspired oxygen fraction (PaFi) less than 300, treatment with colchicine in addition to systemic steroids and SoC had a lower mortality rate compared with steroids and SoC alone[10].

The COLCORONA study is a randomized, double-blind, placebo-controlled trial that included 4488 non-hospitalized covid patients. Results showed that patients who received Colchicine given 0.5mg twice daily for 3 days then once daily for the next 30 days had a lower risk of death and hospitalization compared with those who received placebo[11].

A meta-analysis[12] on the use of colchicine evaluating mortality and risk for mechanical ventilation included 7 studies. Results showed that patients receiving colchicine had a statistically significant lower mortality rate. The risk for mechanical ventilation was also lower in the colchicine group although the difference was not statistically significant.

Recommended Dose

The recommended dose of colchicine used in the completed clinical trials[7-11] is colchicine 1-1.5mg loading dose followed by 0.5mg tab BID for 7-28 days.

Adverse Effects

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

Results of available studies suggest a benefit in the use of colchicine in decreasing mortality, hospitalization and need for mechanical ventilation. More adequately powered clinical trials are needed to clarify the role of colchicine in the management of COVID-19.

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9. H1-ANTIHISTAMINES

Pauline Florence R. Santos Estrella, MD

Introduction

H1-antihistamines has been widely used as treatment of different allergic conditions such as allergic rhinitis, allergic conjunctivitis and urticaria[1]. In 2020, it was speculated that it can be used in the treatment of COVID-19 infection because of its action on mast cells[2]. Mast cells have been hypothesized as the primary source of cytokine release that leads to lung damage in SARS-CoV-2[2].

Aside from its use in allergic inflammatory disorders, antihistamines have been reported to have a potent antiviral activity against Ebola[3] and Influenza viruses[4]. Recently, antihistamines were identified as candidates for further investigation and repurposing as therapeutic agents to treat COVID-19 because of its in vitro antiviral property[5].

Mechanism of Action

H1-antihistamines downregulate allergic inflammation directly through the H1-receptor by interfering with histamine action at H1-receptors on sensory neurons and small blood vessels. Through the ubiquitous transcription factor nuclear factor-kB, they also decrease antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis. In a concentration-dependent manner they inhibit mast cell activation and histamine release[1].

Recently, several in vitro studies were conducted of antihistamines and its antiviral activity against SARS-CoV-2 isolates. Diphenhydramine, Hydroxyzine, and Azelastine exhibited direct antiviral activity against SARS-CoV-2 by binding mechanisms to ACE2 and the sigma receptor-1[5]. Similarly, the inhibitory effect of loratadine and desloratadine on SARS-CoV-2 spike pseudotyped virus' entry into the cell by blocking spike protein–ACE2 interaction was also demonstrated[6]. Azelastine was also reported to have features for binding with the main protease on SARS-CoV-2 in molecular docking and simulation studies[7]. Antiviral tests using native SARS-CoV-2 virus confirmed clemastine and azelastine significantly inhibited SARS2 replication, reducing supernatant viral RNA load with a promising level of activity with clemastine showing the strongest anti-SARS2 activity[8]. These studies therefore suggested that clinical trials may be required to determine if these specific antihistamines have beneficial effects for treatment of COVID-19.

Clinical Studies

There are no clinical trials examining the use of antihistamines alone in the treatment of COVID-19. However, antihistamines combined with low-dose systemic steroids can play a role in the control of COVID-19 related urticarial rashes[9,10].

Conclusion

H1-antihistamines have been known to treat allergic inflammatory disorders and have been shown to have direct antiviral properties. In vitro studies recently demonstrated that they may have an inhibitory action against SARS-Cov-2. These studies may be promising and effective therapeutic options for COVID-19. Clinical trials would be required to establish whether these drugs are effective for treatment of this disease.

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10. HISTAMINE-2 RECEPTOR ANTAGONIST (FAMOTIDINE)

Katrina Faith A. San Gabriel, MD

Introduction

Histamine-2 receptor antagonists (H2 blockers) are widely used in medicine for the suppression of gastric acid production. These drugs typically act by binding to histamine type 2 receptors on the basolateral (antiluminal) surface of gastric parietal cells, interfering with pathways of gastric acid production and secretion.[1]

Mechanisms of Action

Antiviral activity

In a recent study, computational methods to predict structures of proteins encoded by the SARS-CoV-2 genome identified Famotidine as one of the drugs most likely to inhibit the 3-chymotrypsin-like protease (3CLpro) that processes proteins essential for viral replication.[2] Another in silico study revealed that famotidine can interact with the SARS-CoV2 main protease (3CLpro) with a binding free energy of −6.4. It also revealed interaction with two other proteases involved in SARS-CoV2 replication, the viral PLpro and human host Tmprss2 but with lower affinities than for the main protease.[3]

Mast Cell Regulation

A preprint of a newer study proposes that unlike Cimetidine (and other H2 blockers), Famotidine acts as a partial agonist of arrestin recruitment. The drug molecule promotes internalization of the receptor and further non-canonical signaling once internalized through an arrestin-biased mechanism. The authors suggest that mast cell activation and histamine release may be central to lung pathology in patients with COVID-19 and the aforementioned mechanism contributes to the potential benefits of Famotidine therapy. This study has not yet been peer-reviewed.[4]

Clinical Studies

A published retrospective cohort study done in New York, USA concluded that Famotidine use is associated with reduced risk of intubation or death in hospitalized COVID-19 patients. The study identified 1,620 hospitalized patients with COVID-19 including 84 (5.1%) who received famotidine within 24 hours of hospital admission. 340 (21%) patients met the study composite outcome of death or intubation. Propensity score matching was done to balance the baseline characteristics of patients. Use of Famotidine was shown to be associated with reduced risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80). Proton pump inhibitors, which also suppress gastric acid, were not associated with reduced risk for death or intubation.[4]

Another published case series done in New York, USA also suggests that oral famotidine is well tolerated and associated with improved patient-reported outcomes in non-hospitalized patients with COVID-19.Ten consecutive patients with COVID-19 who self-administered high-dose oral Famotidine were identified. Famotidine was well tolerated and all patients reported marked improvements of disease related symptoms after starting Famotidine. The researchers collected longitudinal severity scores of five symptoms (cough, shortness of breath, fatigue, headaches and anosmia) on a four-point ordinal scale modeled on performance status scoring. The combined symptom score improved significantly within 24 hours of starting Famotidine and peripheral oxygen saturation (n=2) and device recorded activity (n=1) increased.[5]

However, the findings of a territory-wide retrospective cohort done on COVID-19 patients in Hong Kong do not support any association between famotidine and COVID- 19 severity. Of the 952 COVID-19 patients included in the study, 51 (5.4%) had severe disease. 23 (2.4%) and 4 (0.4%) patients were given Famotidine and PPIs, respectively. There was no significant association between severe COVID-19 disease and use of famotidine (aOR: 1.34, 95% CI:0.24–6.06; p=0.72) or PPIs (aOR:0.75, 95% CI:0.07–6.00; p=0.80). [6]

Another study is a multicenter retrospective coarsened exact match (CEM) study in 7,158 patients with COVID which measured 30 day all cause mortality.[9] Primary exposure was in-hospital Famotidine use regardless of dose or route within 24 hours of hospital admission. Overall, 687 patients (9.6%) in the prematch cohort and 133 patients (11.5%) in the postmatch cohort died within 30 days of admission. Prematch 30-day mortality was 18.2% of famotidine users versus 8.0% of non-famotidine users (P <.0001). Postmatch 30-day mortality was 15.1% of famotidine users versus 9.5% of non-famotidine users (P <.007). The multivariable logistic regression within the matched cohort showed no association between in-hospital famotidine use and 30-day mortality. The findings did not support the evidence of in-hospital famotidine use on reduced risk of mortality in COVID-19 patients.[9]

Lastly, a retrospective, propensity-matched observational study was done on 878 COVID-19 patients between February 2020 and May 2020 in Hartford Hospital, Connecticut.[10] Use of famotidine (83 patients, 9.3%) was associated with a decreased risk of in-hospital mortality (odds ratio 0.37, 95% confidence interval 0.16-0.86, P = 0.021) and combined death or intubation (odds ratio 0.47, 95% confidence interval 0.23-0.96, P = 0.040). The authors of this observational study concluded that Famotidine use in hospitalized patients with COVID-19 is associated with a lower risk of mortality, lower risk of combined outcome of mortality and intubation, and lower levels of serum markers for severe disease in hospitalized patients with COVID-19.[10]

Recommended Dose

The proposed daily dose of Famotidine in the ongoing clinical trial for hospitalized patients with COVID 19 is 360 mg/day IV (120mg IV q8) for a maximum of 14 days.

The daily oral dose of Famotidine reported in the published case series on non-hospitalized patients with COVID 19 was 60 to 240 mg PO for a median of 11 days (range: 5-21 days).[5]

Adverse Effects

Since its introduction in 1985, Famotidine has been proven to be well tolerated in patients taking the drug for acid-related disorders and has a good safety profile.[7] Common side effects are headache, dizziness, diarrhea or constipation. Famotidine may contribute to QT prolongation particularly when used with other QT-elongating drugs, or in people with poor kidney function.[8]

Conclusion

Famotidine may have beneficial effects in the treatment of patients with COVID-19. However, with conflicting results in currently available literature, better quality studies are needed to verify its effectiveness, efficacy and safety.

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11. HYDROXYCHLOROQUINE (HCQ) and CHLOROQUINE (CQ)

Venjilyn S. Villaver, MD, Ma Lyn R. Benito, MD , Celine N. Yapjuangco, MD

Introduction

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are well-known drugs for their 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*

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.[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]

The WHO in July 2020, upon the recommendation of the Solidarity Trial, agreed to discontinue the trials on the use of Hydroxychloroquine (versus the standard of care) and Lopinavir/Ritonavir (versus standard of care) only in hospitalized patients with COVID-19. However, evaluations on its use in non-hospitalized and pre- and post-exposure prophylaxis are not affected by this decision.[12]

A living systematic review and network meta-analysis done to compare the effects of treatments for COVID-19 showed that hydroxychloroquine might reduce the symptom duration of illness (-4.5 days, low certainty) but also has an increased risk of developing adverse events.[13] A randomized trial of HCQ as post exposure prophylaxis did not differ significantly between participants with HCQ (11.8%) and placebo (14.3%); the absolute difference was -2.4% (95% CI, -7.0 to 2.2; P=0.35). Side effects were more common with HCQ (40.1% vs 16.8%), though not serious.[14]

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

There is only one open-label clinical trial[15] and 2 observational studies.[16,17] 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 results of the study should be interpreted with caution due to the methodologic concerns and a small sample size.[15]

In contrast, a recent multicenter, randomized, open label, three group, controlled trial involving hospitalized patients with suspected or confirmed COVID-19 concluded that the use of hydroxychloroquine, alone or with Azithromycin, did not improve clinical status of the patients.[18]

The Philippine Society for Microbiology and Infectious Diseases (PSMID) has recommended in their interim guidelines NOT to use HCQ except in context of a clinical trial. This holds for post-exposure prophylaxis and in hospitalized, probable or confirmed COVID-19 cases with moderated to severe pneumonia. This recommendation also includes outpatients with early or mild COVID-19 disease.[19]

Several national and society guidelines (China, Italy, Netherlands, Belgium) have initially included HCQ in the management of COVID-19 pneumonia[20,21, 22] before the WHO directives to stop the drug. The latest update of Belgium's guideline no longer recommends its off-label use for COVID-19, except within ongoing clinical registered trials.[22] In a survey of Indian doctors, however, they are still following the national guidelines provided by The Indian National Task Force and they will still recommend HCQ in the management of COVID-19 patients both as prophylaxis and in mild to moderate COVID-19.[23] There are ongoing clinical trials on the use of HCQ or CQ as monotherapy or in combinations for patients with COVID-19.

Adverse Effects

The use of HCQ or CQ in patients with COVID-19 has been associated with QTc prolongation and torsades de pointes.[9, 24] The development of acute renal failure among those given the combination of HCQ and azithromycin was a strong predictor of severe QTc prolongation.[24] 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.[7,8,15,16]

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 the potential for toxicity and lethality when given at high doses. HCQ and CQ should NOT be used in hospitalized COVID-19 patients. Its use in the outpatient setting, for pre and post exposure during the pandemic as interim management for COVID-19 should be weighed versus the risks associated with them.

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12. INOSINE PRANOBEX

Radela Yvonne Ramos Cortes, MD

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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13. INTERFERON and INTERFERON INHIBITORS

Maria Socorro Agcaoili-De Jesus, MD

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]

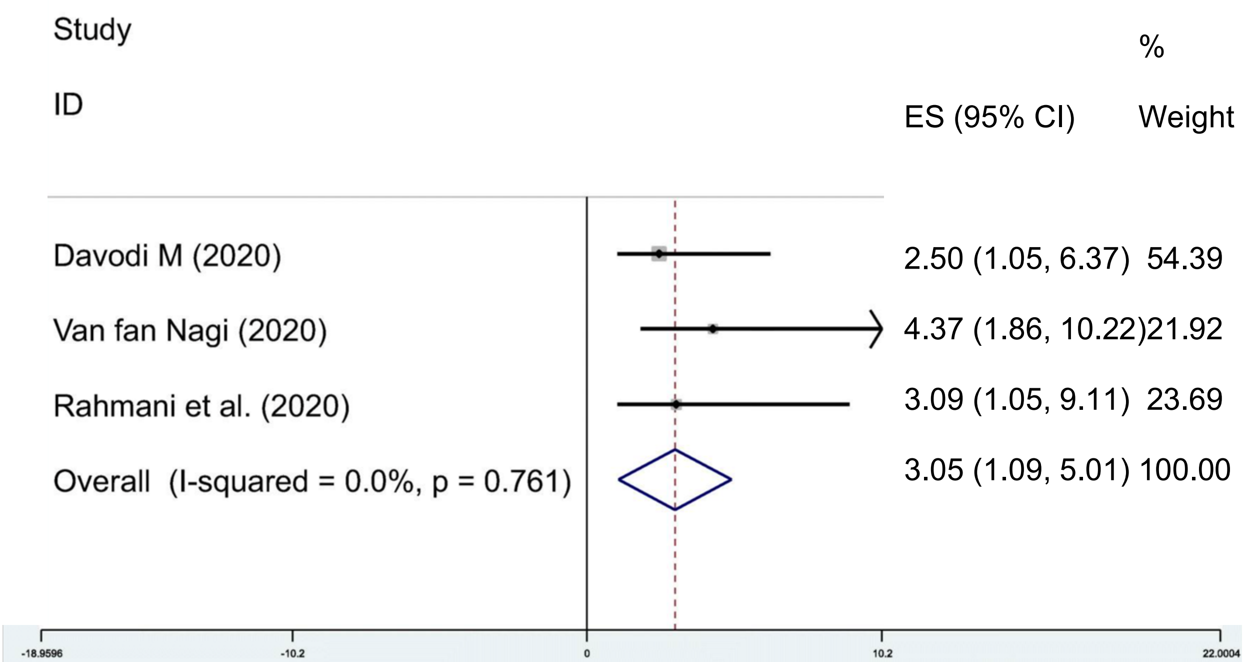
Type I IFNs (IFN-α/β) signal through a receptor complex and triggers a proinflammatory response via the recruitment and activation of immune cells against viral infections. However, this inflammatory reaction can have serious systemic side effects since the IFN receptor is also expressed on all cells. 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

There are only limited clinical trial data available to date specifically evaluating efficacy of interferons for the treatment of COVID-19 infection. [6-12] Most of the studies used IFN β-1a. Some of the studies lacked controlled groups and had small sample size but there are few large controlled trials confirming the effect of interferon in COVID-19.

In one meta-analysis including 3 clinical trials evaluating the prevalence rate of discharged patients, faster discharge rates were significantly associated with the IFN β therapy. A significant difference was found between IFN β and standard of care groups with the overall discharge rate (RR 3.05; 95% CI 1.09-5.01; p=0.761). No significant heterogeneity was found in the study.[13] (Figure 1)



Heterogeneity chi-squared = 0.55 (d.f. =2), P = 0.761
I-squared (variation in ES attributable to heterogeneity) = 0.0%

Figure 1. *Effect of IFN β-1 therapy in COVID-19 patients*

Another meta-analysis of two high risk bias trials randomizing 4,219 patients to Interferon β-1a versus standard of care was done to assess all-cause mortality. Random-effects meta-analysis showed no evidence of a difference between interferon β-1a versus standard care on all-cause mortality (RR 0.75; 95% CI 0.30 to 1.88; p = 0.54). There was significant heterogeneity in the study (I^2 = 84.1%).[14] (Figure 2)

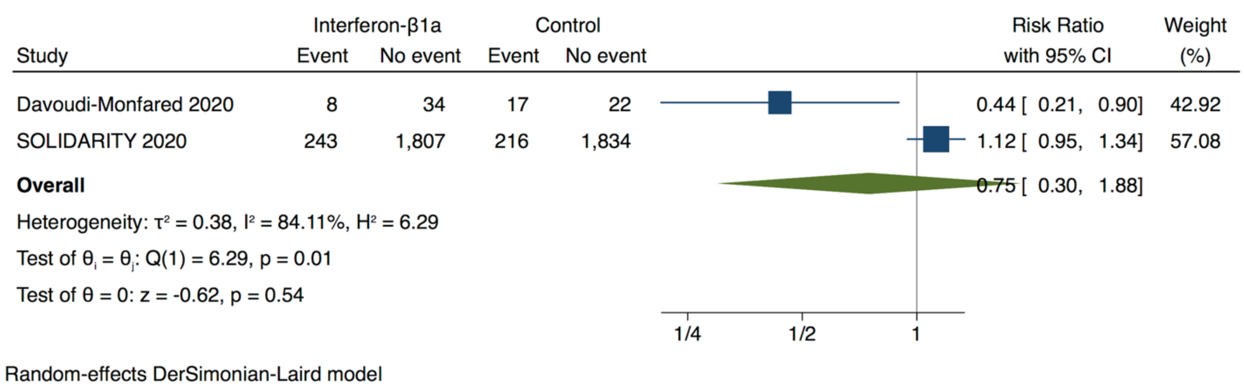


Figure 2. *Effect of Interferon β-1a versus standard care on all-cause mortality*

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.[15] 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.[16]

Recommended Dose

Population	Preparation	Dose
Pedia[16]	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	Interferon α [17]	5 million units or equivalent dose in 2 ml sterile water via vapor inhalation 2x a day for no more than 10 days
	Interferon β-1a [13]	44 micrograms/ml (12 million IU/ml) subcutaneously three times a week for 2 consecutive weeks or until discharge

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.[18]

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%). [19]

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

There were no significant adverse effects or IFN β drawbacks were reported in the different clinical trials. [13,14]

Conclusion

The efficacy and safety of Interferon for the prevention or treatment of COVID-19 is not yet well established. There is insufficient data to recommend either for use or against use of interferon in COVID-19 prevention or treatment.

Interferon alfa via inhalation is included in national guidelines from China as a possible option for treatment of COVID-19.

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14. TARGETED MONOCLONAL ANTIBODIES

A. ANTI-GM-CSF or GM-CSF INHIBITORS

Joanne Michelle I. Mallillin, MD

Introduction

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]

Otilimab is a fully human antibody directed against GM-CSF. It is an investigational drug for rheumatoid arthritis and multiple sclerosis.[9]

Mavrilimumab, a human monoclonal antibody, targets GM-CSF receptor α. It is an experimental drug for rheumatoid arthritis.[10]

Clinical Studies

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

Clinical trials on Lenzilumab, Otilimab, Mavrilimumab and another GM-CSF inhibitor, TJ003234, are currently registered for the treatment of COVID-19 infection. [11]

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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B. ANTI-INTERLEUKIN-1 (IL–1) or IL–1 INHIBITORS

Mary Anne Roldan Castor MD, Marysia Stella T. Recto, MD

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 pro-inflammatory 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]

When the COVID-19 pandemic started, Monteagudo et al. published a retrospective chart review involving five patients diagnosed with MAS (not due to COVID-19) 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]

Since then several case reports of patients with COVID-19 treated successfully with anakinra have been published,[12,13,14,15,16] as well as case series[17,18,19,20,21] and retrospective cohort studies[22,23,24] showing beneficial results. One retrospective cohort study showed benefit with anakinra compared to tocilizumab[25] but another study which reviewed electronic records showed the opposite[26]. A prospective open-label study also showed beneficial results,[27,28] with one study showing improvement only in the inflammatory parameters but not in the clinical outcome[29].

However, last January 2021, the result of the CORIMUNO-ANA-1 multi-center open-label randomized clinical trial among adults hospitalized with COVID-19 and mild-to-moderate pneumonia showed no benefit of anakinra in decreasing the use of non-invasive ventilation, high-flow oxygen, mechanical ventilation. There were also more adverse events in the anakinra group (113 vs. 60; p<0.0004). The data safety monitoring board stopped the trial on the ground of futility.[30] The COVID-19 Living Data, using the CORIMUNO-ANA-1 study, showed inconclusive evidence in terms of clinical improvement (RR 0.97, 95% CI 0.71 to 1.31) and all-cause mortality (RR 0.97, 95% CI 0.49 to 1.90) on Day 28.[31] Another trial, the CORIMUNO-ANA-2, that aims to assess the effect of anakinra in patients with more severe COVID-19 who are in intensive care units has been completed and is still undergoing analysis.[30]

The National Institutes of Health COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as anakinra, for the treatment of COVID-19.[32]

For canakinumab, a retrospective study of 10 patients with COVID-19 treated with canakinumab with hydroxycholorquine and lopinavir/ritonavir showed faster clinical improvement.[33] Several prospective studies also showed clinical improvement.[34,35,36]

There are currently 22 clinical trials registered in ClinicalTrials.gov using anakinra alone or in combination with other immunomodulators, for COVID-19 (including 3 terminated, 1 suspended, 1 completed)[37] and 5 studies using canakinumab (including 1 completed study).[38]

A meta-analysis which included 4 retrospective studies showed significantly lower mortality in the anakinra group (RR 0.26, 95% CI 0.14 to 0.48; I^2 = 0%) and a lower need for mechanical ventilation (RR 0.45, 95% CI 0.25 to 0.82; I^2 = 19%).[39]

	Anakinra		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Cauchois R	0	12	1	10	4.5%	0.28 [0.01, 6.25]
Cavalli G	3	36	7	16	27.0%	0.19 [0.06, 0.64]
Huet T	7	52	22	44	66.4%	0.27 [0.13, 0.57]
Navarro-Millan	1	11	0	3	2.1%	1.00 [0.05, 19.96]
Total (95% CI)		**111**		**73**	**100.0%**	**0.26 [0.14, 0.48]**
Total events	11		30			

Heterogeneity: $Chi^2 = 1.04$, df = 3 (P = 0.79); $I^2 = 0\%$
Test for overall effect: Z = 4.31 (P < 0.0001)

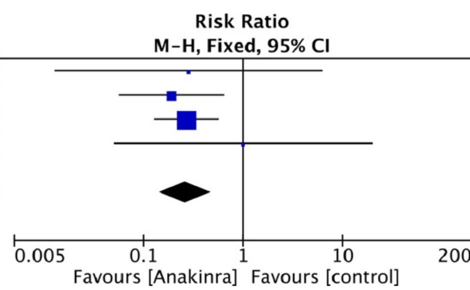

Figure 1*. Forest plot showing mortality risk among patients on anakinra and patients on standard of care.*[39]

	Anakinra		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Cauchois R	2	12	4	10	13.9%	0.42 [0.10, 1.82]
Cavalli G	5	36	1	16	7.5%	2.22 [0.28, 17.52]
Huet T	6	52	18	44	35.3%	0.28 [0.12, 0.65]
Navarro-Millan	5	11	3	3	43.2%	0.52 [0.26, 1.07]
Total (95% CI)		**111**		**73**	**100.0%**	**0.45 [0.25, 0.82]**
Total events	18		26			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.71$, df = 3 (P = 0.29); $I^2 = 19\%$
Test for overall effect: Z = 2.64 (P = 0.008)

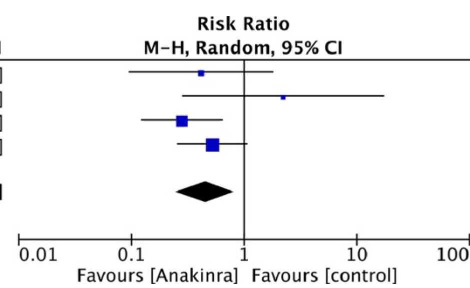

Figure 2*. Forest plot showing risk for need for mechanical ventilation.*[39]

A recent meta-analysis[40] showed that the retrospective study had improved survival (RR 0.24, 95% CI 0.07 to 0.79); there was a wide confidence interval because of the study only involved 29 patients in the anakinra group (this study only included those in the high-dose anakinra group). The overall effect of the 3 prospective studies showed inconclusive result (RR 0.70, 95% CI 0.31 to 1.58, I^2=32.8%).[40]

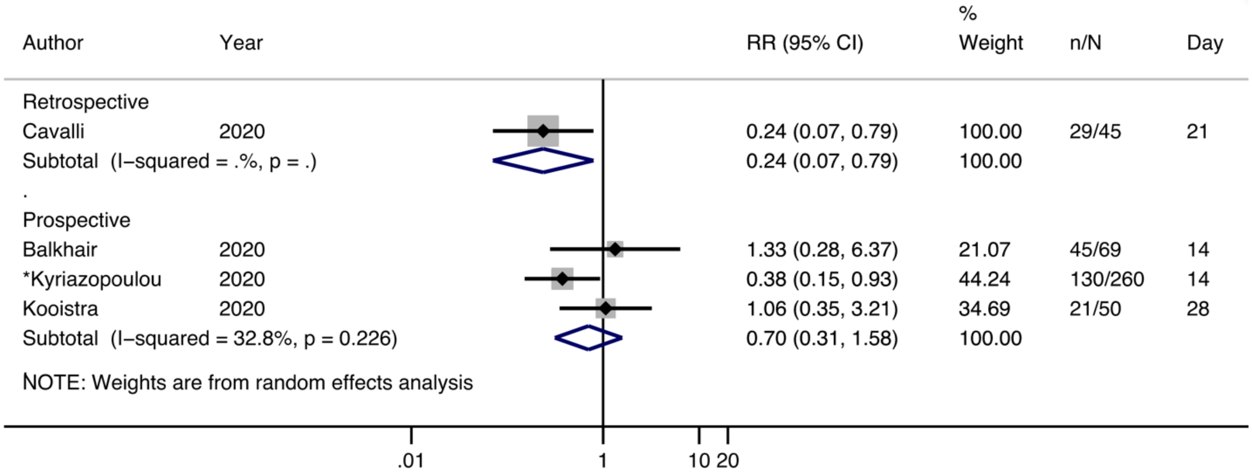

***Figure 3**. Forest plot showing mortality risk among patients on anakinra and patients on standard of care for retrospective and prospective studies.*[40]

Anakinra is also included in the treatment guidelines of Multisystem Inflammatory Syndrome in Children (MIS-C) at a dose of >4 mg/kg/day IV or SQ.[41] However, there are no clinical trials to support the effectiveness of anakinra in patients with MIS-C.

Recommended Dose

In various ongoing clinical trials (in ClinicalTrials.gov[37,38]), the following are the dose ranges used:

Anakinra: 100 mg - 400 mg / day IV (with varying duration)
100 mg / day SC (also with varying duration)
2-4 mg/kg/dose (max 100 mg) IV/SQ Q6-24 hours (for HLH/MAS)[42]
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.[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 high dose anakinra since in one patient the cytopenia returned to normal after dose reduction.[10] The NIH COVID-19 Treatment Guidelines listed the following adverse effects: neutropenia, anaphylaxis, headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, abdominal pain, injection site reactions, and liver enzyme elevations.[32]

Conclusion

Most studies using IL-1 inhibitors are either observational studies or small cohort studies and the meta-analyses are based on these studies. The most recent randomized clinical trial showed no benefit. So, until more clinical trials will show benefit for anakinra, its use for COVID-19 CSS should only be in the context of a clinical research.

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C. ANTI-TNF or TNF INHIBITORS

Cherie C. Ocampo-Cervantes, MD

Introduction

TNF-α plays a role in facilitating the entry of the SARS-CoV into the host cell; thus, anti-TNF-α has been considered as a possible early treatment modality to reduce 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 tumor necrosis factor alpha (TNF- α).[2]

Clinical Studies

There are three ongoing clinical trials for infliximab and one for adalimumab. Another clinical trial for adalimumab from China has been suspended since the pandemic has been controlled in Wuhan, China.

There are currently no recommendations from medical and research agencies on the use of TNF inhibitors for COVID-19.

Recommended Dose

Studies pertaining to the use of TNF inhibitors are very limited.

The study on infliximab uses infliximab or infliximab-abda at 5 mg/kg IV that should be administered within 6 hours of enrollment, and no more than 24 hours following enrollment. Premedication with Paracetamol 650 mg single dose 30 minutes prior to infusion is recommended. Other premedications that may be given include oral Diphenhydramine 50 mg and Prednisone 20 mg, both given 30 minutes prior to infusion. A second dose of infliximab may be given 7-21 days following primary therapy and based on the initial response; the usual treatment schedule is every 2 weeks, this interval is not strictly enforced given the uncertainty of outcomes with primary therapy.[7]

Feldmann et al. have proposed that they should be initiated as early as is practicable.[11]

The study on adalimumab compares between two loading doses of 80 mg and 160 mg.[9]

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.[12] 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.[13]

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.[14]

Conclusion

Studies on the use of TNF inhibitors in COVID-19 are very limited. Clinical trials are still ongoing.

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D. INTERLEUKIN 2

Felicia Racquel S. Tayag, MD

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.

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.

Recommended Dose

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

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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E. JAK 1 & 2 INHIBITORS

Vicky W.E. Biñas, MD, Maria Carmen D. Ang, MD, Michelle Joy B. De Vera, MD

Introduction

JAK 1 and 2 inhibitors currently being studied for the treatment of COVID-19 include baricitinib and ruxolitinib. Baricitinib was licensed in 2018 for treating rheumatoid arthritis with excellent clinical response and no significant safety concerns.[1,2,3] Ruxolitinib was licensed 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 inhibitors of Janus kinases (Jaks) 1 and or 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 and ruxolitinib blocks the production of these cytokines thereby dampens the 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 JAK 1 and 2 inhibitors on cytokine outbreak and additional action of baricitinib on viral entry, it has been suggested that they 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 JAK inhibitors, 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 (e.g., lopinavir or ritonavir and remdesivir) with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters.[10]

Clinical Studies

A systematic review and meta-analysis conducted on the effect of Janus kinase (JAK) inhibition on COVID-19 included three studies (observational, retrospective cohort, prospective cohort open label) on baricitinib and two randomized controlled trials on ruxolitinib. A total of 172 patients received a JAK-inhibitor (treatment group) and 177 received standard of care (control group). The results showed that those patients in the treatment group had significantly reduced odds of mortality (OR, 0.12; 95% CI, 0.03–0.39, p< 0.001) and ICU admission (OR, 0.05; 95% CI, 0.01–0.26, p< 0.001), and had significantly increased odds of hospital discharge at 2 weeks (OR, 22.76; 95% CI, 10.68–48.54, p< 0.00001) compared with the control group. However, there was no significant difference between the control and treatment groups regarding patients needing mechanical ventilation or developing ARDS, (Figure 1).[11]

The Adaptive COVID-19 Treatment Trial-2 (ACTT-2), a double-blind, randomized, placebo-controlled study was conducted by Kalil et al and included 1,033 moderate-severe COVID-19 patients with a mean age of 55.4 years. Five hundred fifteen (515) patients were randomly assigned to the treatment group (baricitinib plus remdesivir) while 518 patients to the control group (remdesivir plus placebo). The results showed that the median time to recovery was 7 days (95% confidence interval [CI], 6 to 8) in the treatment group and 8 days (95% CI, 7 to 9) in the control group. The rate ratio for recovery was 1.16; (95% CI, 1.01 to 1.32; P = 0.03), with 30% higher odds of clinical improvement at day 15 in the treatment group (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients who received high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days in the treatment group and 18 days in the control group (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). The 28-day mortality was 5.1% in the treatment group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). Serious adverse events were noted to be less frequent in the treatment group as compared to the control group (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; P = 0.03). New infections were likewise less frequent (5.9% vs. 11.2%; difference, −5.3 percentage points; 95% CI, −8.7 to −1.9; P = 0.003).[12]

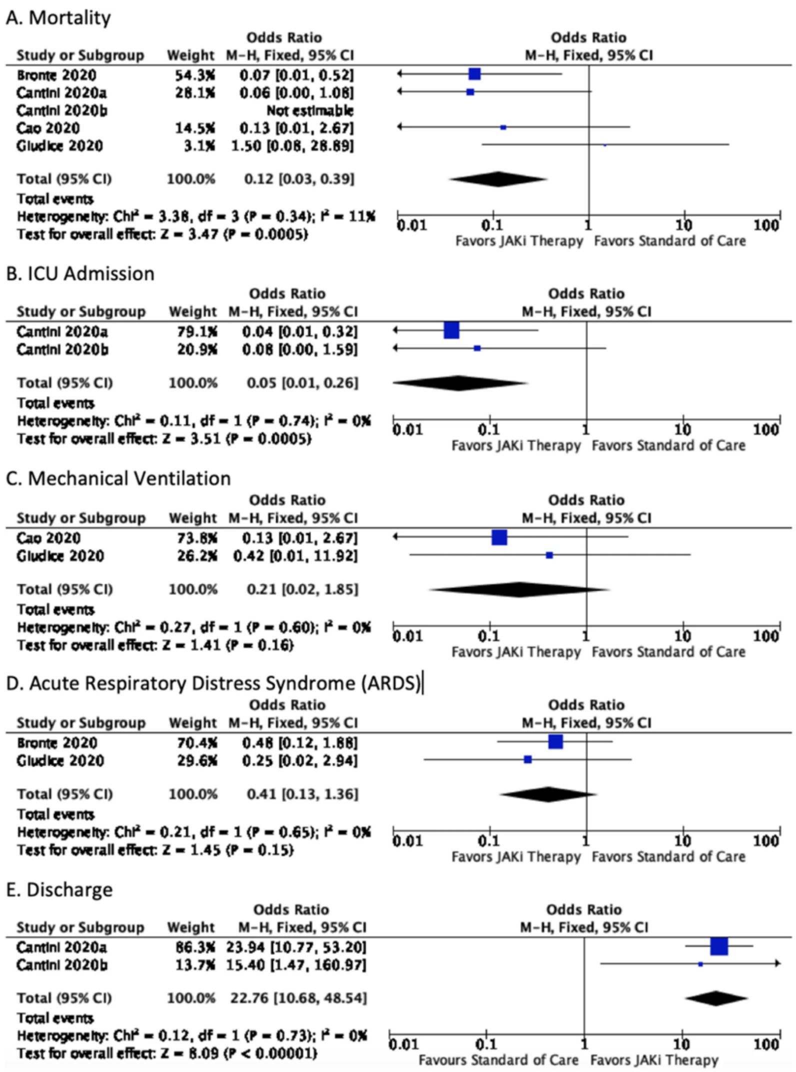

Figure 1. *Mortality, ICU Admission, Requirement of Mechanical Ventilation, ARDS, and Discharge of patients treated with JAK-inhibitor.*

The use of baricitinib plus remdesivir may be effective in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[13] On November 19, 2020, the U.S. FDA issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in the treatment of COVID-19 in these group of patients if corticosteroids cannot be used.

Currently, there are 9 ongoing studies on baricitinib and 11 on ruxolitinib that are registered in clinical trials.gov.

Recommended Dose

Baricitinib:[14]

Adults and pediatric patients $\geq$ 9 years old: 4 mg once daily
Pedaitric patients 2 to < 9 years old: 2 mg once daily
Administer orally or through nasogastric tube
Recommended total treatment duration: 14 days or until hospital discharge whichever comes first
Dosage adjustments are recommended in patients with laboratory abnormalities, including renal impairment

Ruxolitinib:[15]

Adult dose: 5 or 10 mg orally twice daily for 14 days
Pediatric dose ≤12 y/o: Safety and efficacy not established

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.[14] 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.[15]

Baricitinib is not recommended for patients on hemodialysis, have end stage renal disease (EGFR < 15ml/min/1.73 m^2), have acute kidney injury and those with active tuberculosis. It is not advisable to use it in combination with systemic corticosteroids, since both can suppress the immune system and increase the risk of infection.

Conclusion

A systematic review and meta-analysis that included 3 studies on baricitinib and 2 studies on ruxolitinib showed promising outcomes on their use in moderate-severe COVID-19.

Findings of the ongoing studies may further elucidate the relationship between clinical outcomes and Janus kinase-inhibitors in this setting.

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15. MESENCHYMAL STEM (STROMAL) CELLS

Michelle Joy B. De Vera, MD

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 are 2 completed phase 1/2 randomized controlled trials published using MSC for COVID-19 infections. Primary outcome for both studies were safety of MSC [5,6], and altered proportion of whole lung lesion volumes from baseline to day 28. [6] Results suggest that MSC treatment is a safe and potentially effective therapeutic approach for COVID-19 patients with COVID-19 pneumonia. There were no increased occurrence of pre-specified infusion-associated adverse events within 6 hours from each infusion, nor cardiac arrest or death within 24 hours post infusion, [5] or any adverse events (abnormal laboratory tests, dizziness, cough etc). [6] In addition, the Lanzoni et al study showed MSC decreased inflammatory cytokines and improved patient survival [5], while the Shi, et all study showed improved lung damage after MSC administration. [6]

In the Philippines, a case series published on 11 patients with moderate to severe COVID-19 pneumonia showed that MSC therapy decreased inflammatory cytokines and may improve clinical status without any infusion related reaction. [7]

Adverse Reactions

Safety and effectiveness of MSCs have been documented in several clinical trials. [8,9] However, numerous complications have been reported from improper application of stem cells. [10] 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. [11]

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[11].

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.

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16. MYCOPHENOLATE MOFETIL

Tara T. Rivera, MD

Introduction

Mycophenolate mofetil (MMF) is derived from mycophenolic acid (MPA), an antineoplastic antibiotic isolated from different species of *Penicillium* fungi.[1] It is used mainly for its immunosuppressive properties in solid organ transplant patients to prevent or treat allograft rejection.[2] Other indications for its use are autoimmune disorders (e.g. lupus nephritis, myositis syndromes, or Crohn's disease), small or large vessel vasculitides, or various skin conditions.[3]

In-vitro studies have shown antiviral activity of MPA against both Middle East respiratory syndrome coronavirus (MERS-CoV)[4,5,6] and SARS-CoV-2.[7] Clinical studies to support these findings, however, are lacking.

Mechanism of Action

Mycophenolic acid (MPA), the active component of MMF, acts as an immunosuppresant by targeting cell-mediated and humoral immune responses. Aside from preventing human B and T lymphocyte proliferation by inhibiting conversion of inosine monophosphate to guanosine monophosphate,[8] it has also been found to affect lymphocyte function through various mechanisms. In vitro studies have shown MPA downregulating cell adhesion molecules of T lymphocytes, inhibiting T cell proliferation in response to mitogens, and inhibiting expression of interferon gamma in murine T cells.[8,9,10] Similarly, MPA blocked human plasma cell differentiation, and antibody production by human B lymphocytes.[11]

In addition to its immunomodulating properties, antiviral activity has been demonstrated by MPA against MERS-CoV.[4,6] A proposed mechanism for this is the inhibition of an enzyme found in coronaviruses. Papain-like protease (Pl^{pro}) is an enzyme necessary for viral maturation and survival against the host's interferon reponse. MPA has been found to inhibit MERS-CoV Pl^{pro} activity. However, the same study demonstrated that MPA had no effect on SARS-CoV Pl^{pro}.[6] An in vitro study years later on SARS-CoV-2 showed that MPA did not prevent viral growth by the cytopathic effect method. SARS-CoV-2 replication, however, was inhibited 100-fold at low effective concetrations.[7]

Clinical Studies

No human studies have been done to determine whether MPA's immunomodulatory or antiviral properties have an effect on SARS-CoV-2 or COVID-19.

A related study done was a retrospective cohort of 51 patients with MERS-CoV infection. Survival was associated with treatment with mycophenolate mofetil.[12] Important to note, however, that mycophenolate mofetil was given to less severely ill patients, and was given in combination with interferon beta, another immunomodulator, in 7 out of 8 patients.

Adverse Effects

Mycophenolate mofetil is associated with nausea, diarrhea, abdominal pain, anemia, headache, hypertension, leukopenia, thrombocytopenia, or a predisposition to developing infections.[2] It is also less commonly associated with hepatotoxicity, which is in most cases mild and self-limited.[2,13]

Conclusion

While a few in vitro studies may have demonstrated the antiviral activity of MMF against MERS-CoV and SARS-CoV-2, there is insufficient clinical evidence to determine its efficacy and safety against COVID-19. More high quality researches are needed to establish the role of MMF in treating COVID-19.

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17. RELEASE ACTIVE ANTIBODIES TO HUMAN INTERFERON GAMMA

Kristine Marie F. Gutierrez, MD

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 been 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. <u>STATINS</u>

Maria Carmen D. Ang, MD

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 COVID-19 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

Although currently there is no clinical evidence of the beneficial use of statins in COVID-19 patients, seven studies are underway.

Recommended Dose

Adults: Atorvastatin 20-40mg once a day
Rosuvastatin 20mg once a day
Pravastatin 80mg once a day
Simvastatin 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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SUPPLEMENTS

1. MELATONIN

Pascualito I. Concepcion, MD and Radela Yvonne Ramos-Cortes, MD

Introduction

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

Mechanism of Action

As an anti-inflammatory, 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.[1,2,3]

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.[5,6]

Lastly, melatonin improves proliferation and maturation of NK cells, T and B lymphocytes.[7]

Clinical Studies

There is one case series by Castillo, R. et al that looked at the effect of melatonin on 10 COVID-19 patients. This study concluded that high-dose melatonin may play a role as adjuvant therapy against COVID-19.[8] These findings are in conjunction with published expert's recommendations to give melatonin to COVID-19 patients on the basis of its immunologic mechanism of action.

However, given the small sample size and methodological design, the results of this study must be taken with caution.

Recommended Dosing:

Though there are a lot of debates about the recommended dose of melatonin fpr treating COVID-19 patients, an approved dosage for this purpose does not yet exist.

Adverse Effects

Adverse effects include fatigue, changes in mood, psychomotor or neurocognitive performance.[9]

Conclusion

There are many published articles that recommend the giving of melatonin as adjunct treatment for COVID-19, however, there are no yet clinical studies that can conclusively support these claims.

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2. OMEGA 3 FATTY ACID AND DHA

Caroline T. Gloria, MD and Radela Yvonne Ramos Cortes, MD

Introduction

Omega-3 Fatty acid, including Docosahexaenoic acid (DHA) a long-chain omega-3 fatty acid, is 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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3. PROBIOTICS

Caroline T. Gloria, MD and Cesar Joseph C. Gloria, MD

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

2×10^9 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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4. QUERCETIN

Caroline T. Gloria, MD and Cesar Joseph C. Gloria, MD

Introduction

Quercetin has an interesting inhibitory effect on inflammatory responses.

Mechanism of Action

Quercetin not only inhibits the production of NLRP3 inflammasome components and pro-IL-1β, but also suppresses inflammation through interference in various signaling pathways, especially NF-κB, eventually suppressing inflammation.

It also has an inhibitory effect on TH17, another proinflammatory cytokine.

Gut microbiota has an unparalleled function in the regulation of immune responses and the development of a variety of diseases caused by aberrant immune responses. The effect of quercetin to correct dysbiosis can help control systemic inflammation in the body. Finally, quercetin, as an anti-inflammatory, antioxidant, analgesic and NLRP3 inflammasome inhibitor compound, can be a potential treatment for severe inflammation, which is the main life-threatening condition in patients with COVID-19.[1]

Clinical Studies

There are ongoing and unpublished clinical trials[1,2] on quercetin for COVID-19 immunomodulation.

Recommended Dose

Two 500mg tablets daily, the duration, though, is not indicated.

Adverse Effects

Oral supplementation with quercetin up to 1 g/day for 3 months has not resulted in significant adverse effects[3]. In a randomized placebo-controlled study, 30 patients with chronic prostatitis were supplemented with oral quercetin (1 g/day) and reported only two mild adverse reactions (headache and temporary peripheral paresthesia)[4]. Intravenous administration of quercetin in a phase I clinical trial for cancer patients resulted in nausea, vomiting, sweating, flushing, and dyspnea at doses >10.5 mg/Kg (756 mg per 70 Kg individual)[5]. Only higher intravenously administered doses up to 51.3 mg/Kg (around 3,591 mg per individual) were associated with renal toxicity[3]. The safety of quercetin-based oral supplementation during pregnancy and breastfeeding has not been established.

Conclusion

Quercetin, as an anti-inflammatory, antioxidant, analgesic and NLRP3 inflammasome inhibitor compound, can be a potential treatment for severe inflammation, which is the main life-threatening condition in patients with COVID-19. More studies, however, are needed to determine its role in the management of COVID-19.

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5. VIRGIN COCONUT OIL (LAURIC ACID)

Lara Theresa A. Aleta, MD

Introduction

Virgin coconut oil (VCO) is extracted from the *Cocos nucifera* plant by the wet milling process and has been, for many years, proven to have antiviral effects. Lauric acid and its derivatives monolaurin, and sodium lauryl sulfate (which is also known as sodium dodecyl sulfate) compose 50% of coconut oil and are responsible for coconut oil's antiviral and immunomodulatory effects.[1]

Mechanism of Action

Three mechanisms have been proposed to explain the antiviral activity of lauric acid and monolaurin: (1) they cause disintegration of the virus envelope; (2) they can inhibit late maturation stage in the virus replicative cycle (3) they can prevent the binding of viral proteins to the host cell membrane. [1,2,3,4,5,6]

As an immunomodulator, VCO has been shown to increase CD4 counts[7] and to increase the ratio of IFNγmRNA to IL-4 mRNA.[8]

Clinical Studies

There are ongoing clinical studies on the use of VCO as an oral supplement for COVID-19 in the Philippines as initiated by the Department of Science and Technology (DOST)

Recommended Dose

As a topical agent, coconut oil can be used ad libitum. As an oral supplement, no standard dose has been established.

Adverse Effects

Coconut oil and its derivatives have been shown to be safe in humans and animals. [1]

Conclusion

More clinical trials are needed to establish its efficacy for COVID-19.

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6. VITAMIN C

Beatrice S. Vicente Pascual, MD

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

According to the NIH COVID-19 Treatment Guidelines[7] there are insufficient data for the Panel to recommend the use of vitamin C for the treatment of COVID-19 in critically ill or non-critically ill patients.

Adverse Effects

High dose Vitamin C side effects are calcium oxalate nephropathy and elevation in blood sugar.[8]

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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7. VITAMIN D

Beatrice S. Vicente Pascual, MD

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]

Calcitriol, (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, calcitriol promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes.[7]

The role of vitamin D in COVID-19 infection is twofold. First, vitamin D supports the production of antimicrobial peptides in the respiratory epithelium, thus making infection with the virus and development of COVID-19 symptoms less likely.[8] Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2. Deregulation of this response, especially of the renin– angiotensin system, is characteristic of COVID-19 and the degree of overactivation is associated with poorer prognosis. Vitamin D is known to interact with a protein in this pathway—angiotensin converting enzyme 2 (ACE2)—which is also exploited by SARS-CoV-2 as an entry receptor. Vitamin D promotes expression of ACE2 contrary to the downregulation of ACE2 by the SARS-CoV-2.[8]

Clinical Studies

Among hospitalized patients with COVID-19, a single high dose of vitamin D_3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19.[9]

Recommended Dose: [1,10]

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.[11]

Conclusion

There is not enough evidence to recommend using Vitamin D for treating COVID-19. Future studies should be high quality randomized controlled trials to determine the clinical effectiveness of Vitamin D supplements as adjunctive treatment for COVID-19.

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8. ZINC

Beatrice S. Vicente Pascual, MD

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]

The study looked to determine whether high dose zinc and/or high-dose vitamin C reduced the severity or duration of COVID-19 compared to standard outpatient care. This was a multicenter, single health system randomized clinical factorial open-label trial of 214 patients with confirmed COVID-19 infections. Patients were randomized to either receive 10 days of zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard of care. It was found that none of the interventions significantly decreased the duration of COVID-19 symptoms compared to standard of care.[3]

As of the present time, the COVID-19 Treatment Guidelines Panel **recommends against** using **zinc** supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.[4]

Recommended Dose

Not yet established for COVID-19.

Dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.[5]

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.[6]

Conclusion

There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.[6]

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CONCLUDING REMARKS

The SARS-CoV-2 virus has evolved over time. Currently, there are new variants that have been discovered. These variants have led to more cases of COVID-19 resulting in the continued strain in health care resources, hospitalizations and death. As of August 15, 2021, the Department of Health of the Philippines reported that 1,741,616 people have had COVID-19 in the country. 30,340 are known to have died from the disease. The members of the Philippine Society of Allergy, Asthma and Immunology, Inc. continue their mission to review the literature on the various immunomodulators that may be used in the management of moderate to severe COVID-19 cases and weed out drugs which do not seem to show benefit.

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 4.2 version dated August 15, 2021. Typographical errors present in the previous version were corrected.

Acknowledgement:

- The Philippine College of Physicians and the Philippine Pediatric Society for recognizing and supporting this project.
- All the health care workers who continue to risk their lives so that we may continue to learn and improve.
- All the scientists who developed and tested the various COVID-19 vaccines to allow us to move forward with hope.

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APPENDICES

Appendix 1. Availability of the Immunomodulators in the Philippines

Appendix 2. List of Authors and their Academic Position or Hospital Affiliation

1. AVAILABILITY OF THE IMMUNOMODULATORS IN THE PHILIPPINES

From Published Studies

	Available	**Not available**
Polyclonal antibody-based agents	Intravenous Immunoglobulin Convalescent plasma	
ACE Inhibitor	Lisinopril Ramipril Enalapril Captopril	
Alpha-1 Adrenergic Receptor Antagonist	Prazosin	
Angiotensin II Receptor Blockers	Losartan Valsartan	
Anticoagulants	Apixaban Bemiparin Dabigatran Dalteparin Enoxaparin Fondaripanux Unfractionated Heparin Nadroparin Rivaroxaban Tinzaparin	
Anti-IL1		Anakinra
Anti-IL6	Tocilizumab	
Anti-CCR5	Leronlimab	
Anti-Fibrotic	Pirfenidone	
Anti-TNF	Adalimumab	
Anti-malarial agents	Hydroxychloroquine Chloroquine	
Anti-parasitic agent	Ivermectin	
Anti-viral Agents	Lopinavir/Ritonavir Remdesivir Favipiravir	Ribavirin Umifenovir (Arbidol)
BTK Inhibitors	Ibrutinib	
Calcineurin Inhibitors	Cyclosporin A Tacrolimus	
Corticosteroid	Dexamethasone Methylprednisolone Prednisone Hydrocortisone	
H2 Blocker	Famotidine	
Interferons	IFN α, IFN β (for injection)	IFN α, IFN β (inhalatational)
JAK Inhibitors	Baricitinib	
Macrolide	Azithromycin	
Traditional Chinese Medicine	Lianhua Qingwen	

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2. AUTHORS AND THEIR ACADEMIC POSITION OR HOSPITAL AFFILIATION

- **Jovilia M. Abong, MD**
  Professor 1, De La Salle Medical Health Sciences Institute University Medical Center
- **Maria Socorro Agcaoili De-Jesus, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Maria Carmela Agustin Kasala, MD**
  Consultant, The Medical City
- **Lara Theresa A. Aleta, MD**
  Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Eileen Simone Alikpala Cuajunco, MD**
  Clinical Faculty, Ateneo School of Medicine and Public Health – The Medical City
- **Maria Carmen D. Ang, MD**
  Consultant, San Pedro Hospital Davao City
- **Ma. Fredelita C. Asuncion, MD**
  Consultant, Cardinal Santos Medical Center
- **Ma. Lyn R. Benito, MD**
  Consultant, Makati Medical Center
- **Vicky W.E. Biñas, MD**
  Assistant Professor 4, De La Salle Medical Health Sciences Institute University Medical Center
- **Maria Zoila G. Carandang, MD**
  Assistant Professor, College of Medicine, Pamantasan ng Lungsod ng Maynila
- **Mary Anne R. Castor, MD**
  Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Pascualito I. Concepcion, MD**
  Associate Dean for Academics, Ateneo de Zamboanga University School of Medicine
- **Julia C. De Leon, MD**
  Consultant, Cardinal Santos Medical Center
- **Michelle Joy B. De Vera, MD**
  Associate Professor, Ateneo School of Medicine and Public Health – The Medical City
- **Regina Dionisio Capulong, MD**
  Consultant, Medical Center Manila
- **Maria Cristina R. Edquilag, MD**
  Associate Professor 1, College of Medicine Pamantasan ng Lungsod ng Maynila-OMMC
- **Aileen A. Elorde, MD**
  Chair, Community Pediatrics, Davao Doctors Hospital
- **Mary Anne Fran-Cuaresma, MD**
  Consultant, Medical Center Taguig
- **Caroline T. Gloria, MD**
  Consultant, Asian Hospital and Medical Center
- **Cesar Joseph C. Gloria, MD**
  Consultant, St. Luke’s Medical Center Bonifacio Global City
- **Kristine Marie F. Gutierrez, MD**
  Instructor V, University of Santo Tomas Faculty of Medicine and Surgery
- **Roxanne C. Hao, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Rommel Crisenio M. Lobo, MD**
  Head, Section of Allergy Asthma and Immunology, Fe del Mundo Medical Center
- **Eden P. Macalalag, MD**
  Consultant, St. Luke’s Medical Center
- **Joanne Michelle I. Mallillin, MD**
  Consultant, Our Lady of the Pillar Medical Center
- **Alric V. Mondragon, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Aimee Lou M. Nano, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Cherie C. Ocampo-Cervantes, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Alejandro P. Ortigas, MD**
  Consultant, St. Luke’s Medical Center
- **Jenifer R. Otadoy-Agustin, MD**
  Clinical Associate Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Ma. Stella G. Paspe, MD**
  Consultant, Western Visayas Medical Center
- **Radela Yvonne Ramos Cortes, MD**
  Consultant, Riverside Medical Center
- **Melissa Anne G. Rapadas-Aguirre, MD**
  Consultant, Metro Davao Medical and Research Center
- **Marysia Stella T. Recto, MD**
  Professor, University of the Philippines College of Medicine – Philippine General Hospital
- **Tara T. Rivera, MD**
  Consultant, Medical Center Manila

- **Katrina Faith A. San Gabriel, MD**
  Consultant, Divine Word Hospital, Tacloban
- **Pauline Florence R. Santos Estrella, MD**
  Consultant, Rizal Medical Center
- **Fatima Johanna T. Santos-Ocampo, MD**
  Head, Section of Allergy and Immunology, Department of Pediatrics, Makati Medical Center
- **Jennifer Serrano-Flores, MD**
  Chairman, Department of Pediatrics, San Pablo Doctors Hospital
- **Ivy June Minerva Soriano, MD**
  Active Staff, West Visayas State University – Medical Center
- **Frances M. Tan, MD**
  Chair, Research Committee, Victor R. Potenciano Medical Center
- **Felicia Racquel S. Tayag, MD**
  Consultant, The Medical City
- **Mary Grace V. Toledo, MD**
  Lecturer, Central Philippine University
- **Maria Rowena B. Valerio, MD**
  Consultant, Dr. Amando Garcia Medical Center
- **Beatrice S. Vicente Pascual, MD**
  Consultant, Angeles University Foundation Medical Center
- **Venjilyn S. Villaver, MD**
  Instructor, University of Santo Tomas Faculty of Medicine and Surgery
- **Celine N. Yapjuangco, MD**
  Associate Professsor 1 University of Perpetual Delta Medical Center
- **Cynthia Purificacion Ybiernas-Gallinero, MD**
  Training Officer, Department of Pediatrics, St. Paul's Hospital

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