Philippine Society of Allergy, Asthma and Immunology, Inc.

A REVIEW OF IMMUNOMODULATORS AS THERAPEUTIC INTERVENTIONS FOR MODERATE TO SEVERE COVID-19 INFECTIONS (Version 3.0, September 20, 2020)

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

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

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

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

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

Understanding the pathophysiology of COVID-19 is imperative for the clinician to provide timely and appropriate treatment for each patient. Siddiqi and Mehra proposed a 3-stage classification of disease progression with distinct clinical findings, response to therapy and clinical outcomes. (Figure 1)[7] Stage 1 is the early infection (mild) stage, wherein the virus gains entrance to the body, incubates and attaches to the angiotensin converting enzyme receptor 2 (ACE2) which is also the SARS-CoV-2 receptor. These are found in lung, intestinal, and vascular epithelia. There is a rapid viral replication in the cells with eventual apoptotic (non-inflammatory) and pyroptotic (inflammatory) cell death targeting the T and B lymphocytes. This explains the lymphopenia noted at this stage, which can contribute to decreased viral clearance, and worsening of disease.

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

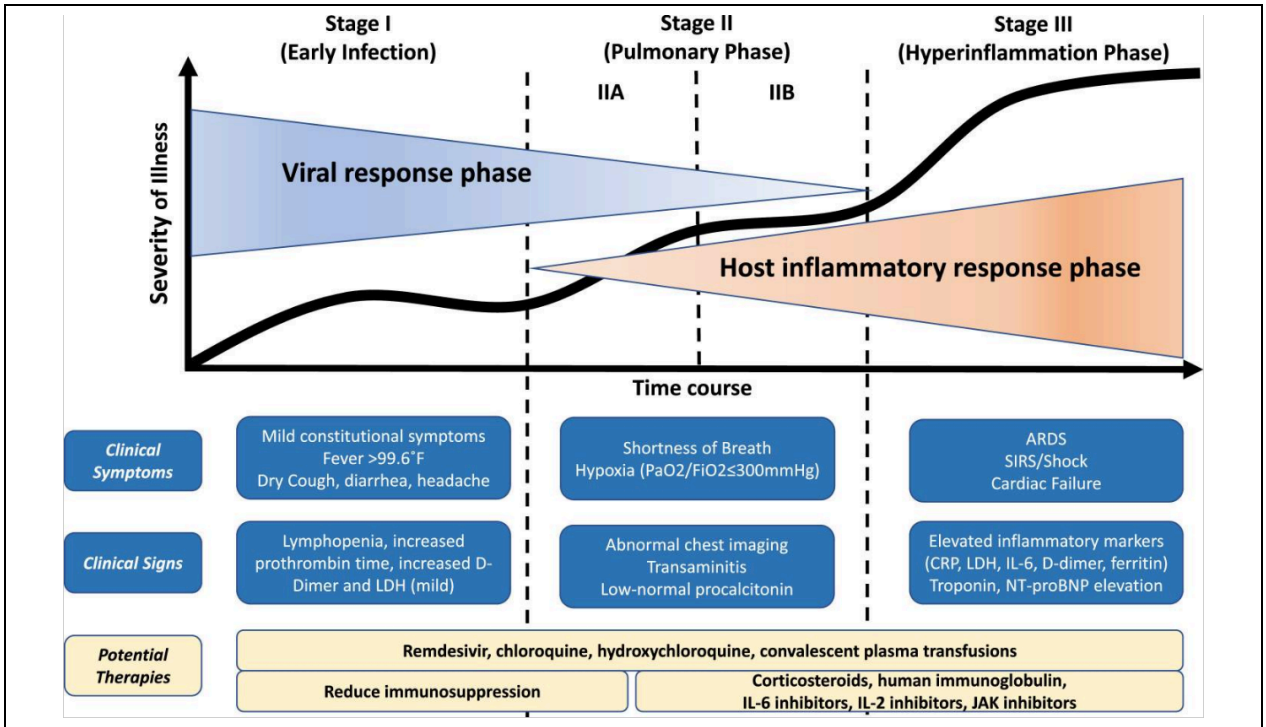

Figure 1. Classification of COVID-19 Disease States and Potential Therapeutic Targets
The figure shows 3 escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome, CRP=C-reactive protein;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

Viral neutralizing antibodies (vNAB) are developed which should prevent viral endocytosis into cells and enable clearance of virus. However, in some individuals, vNAB can attach to Fc receptors on macrophages/monocytes leading to antibody-dependent enhancement of viral activity. This phenomenon leads to suboptimal anti-viral clearance, persistent viral replication and inflammation.[8] This stage occurs around 7–14 days after the onset of the symptoms when the virus starts a second attack. Clinically, this is characterized by worsening of symptoms with dyspnea, worsening of pulmonary lesions and development of hypercoagulable state with ischemic changes such as ecchymosis of the fingers and toes together with the worsening of heart and kidney functions. Inflammation, infection and other factors can lead to excessive activation of coagulation.

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

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

In a recent article in *The Lancet*, Huang et al. studied the clinical features of 41 patients infected with 2019 novel coronavirus needing admission in a designated hospital in Wuhan, China.[11] These patients were noted to have high amounts of IL1B, IFNγ, IP10, and MCP1, probably leading to activated T-helper-1 (Th1) cell responses. Moreover, patients requiring ICU admission had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNFα than those not requiring ICU admission, suggesting that the cytokine storm was associated with disease severity.[11] This also implies that several cytokines may need to be targeted when trying to control the cytokine storm.

The cytokine storm can progress in stages. In the early stage of infection, there is an elevated amount of IL-1 beta and tumor necrosis factor (TNF). They proliferate in the early minutes to a few hours of infection. This acute response triggers the proliferation of IL-6 and IL-18 which promotes a more sustained pro-inflammatory state. IL-10

appears later causing a negative feedback to IL-6. The IL-10 reaction is the body's attempt to control inflammation and is also termed "immunoparalysis".[8] However, it has been suggested that patients who survive the initial cytokine storm but subsequently die may be those who do not recover from immunoparalysis. This may be genetically determined.[12] When this happens, antiviral therapies may no longer be effective and immunotherapy via immunomodulation of the host response may be necessary to reverse the ongoing inflammation. Immunomodulation must, then, be instituted early enough to prevent the cytokine storm.

Some parameters may indicate the onset of the cytokine storm in COVID-19 infections. It is proposed that early initiation of immunomodulation during the period preceding the cytokine storm will lead to more successful treatment outcomes. In a retrospective study of 11 critically ill Chinese patients with COVID pneumonia, the following were noted to be high risk factors of cytokine storm:[13]

1) 50% or greater area of lung injury
2) Decreased CD4 and CD8 T lymphocyte counts (lower than 50% of minimum normal range values)
3) Increased levels of IL-6

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

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

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

REFERENCES:

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5(4):536-44 in BMJ Best Practice.
2. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. 2020. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.
3. Minoia F, Davi S, Alongi A, et al. Criteria for cytokine storm syndromes. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. p.61-79.
4. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393. doi: 10.1016/j.clim.2020.108393. [Epub ahead of print]
5. Nelson RP, Ballow M, Bellanti JA. Advances in clinical immunomodulation: In Immunology IV Clinical Applications in Health and Disease. Bellanti, JA (ed) Bethesda, Maryland: I care Press, 2012. pp. 389-422
6. Pirofski LA, Casadevall A. Immunomodulators as an antimicrobial tool. Current Opinion in Microbiology 2006;9 :489-495.
7. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020. doi: 10.1016/j.healun.2020.03.012. [Epub ahead of print].
8. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. doi: 10.1007/s12250-020-00207-4. [Epub ahead of print].
9. Shimizu M. Clinical features of cytokine storm syndromes. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. p.31-41.
10. Magro C et al. Complement-associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Translational Research 2020.doi:10.1016/j.trsl.2020.04.007. [Epub ahead of print].
11. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497–506. doi: 10.1016/S0140-6736(20)30183-5.
12. Schulert GS, Zhang K. Genetics of acquired cytokine storm syndromes. In: Cytokine Storm Syndrome. Cron RQ, Behrens EM (editors). Cham, Switzerland: Springer International Publishing; 2019. p.113-130.
13. Favalli EG, Ingegnoli F, De Lucia O et al. COVID-19 Infection and rheumatoid arthritis: faraway, so close. Autoimmunity Reviews. 2020; 19: 102523. doi.org/10.1016/j.autrev.2020.102523

IMMUNOMODULATORS FOR COVID-19

A. Pathogen-Specific Immunomodulators (Polyclonal Antibody-Based Agents)
   1. Intravenous Immunoglobulin (IVIG)
   2. Convalescent Plasma
   3. Hyperimmune Globulin

B. Non-Pathogen-Specific Immunomodulators
   1. ACE Inhibitors and Angiotensin Receptor Blockers
   2. Alpha 1 Adrenergic Receptor Antagonists
   3. Anti-Viral Agents
      a. Favipiravir / T-705/ Favipira/ Favilavir
      b. Lopinavir/Ritonavir (Lpv/R)
      c. Oseltamivir
      d. Remdesivir/ Rdv/ GS-5734
      e. Ribavirin/Rbv
      f. Umifenovir (Arbidol)
   4. Aspirin
   5. Azathioprine
   6. Azithromycin
   7. BCG Vaccine
   8. Calcineurin Inhibitors (Cyclosporine, Tacrolimus)
   9. Colchicine
   10. Corticosteroids
   11. Hydroxychloroquine & Chloroquine
   12. Inosine Pranobex
   13. Interferon and Interferon Inhibitors
   14. Targeted Monoclonal antibodies (Cytokine Antagonists)
      a. Anti-GM-CSF (lenzilumab)
      b. Anti-IL-1 (anakinra, rilonacept, canakinumab)
      c. Anti-IL-6 (tocilizumab, siltuximab, sarilumab)
      d. Anti-TNF (adalimumab)
      e. CCR-5 inhibitor (leronlimab)
      f. IL-2 (aldesleukin)
      g. JAK-1 and 2 inhibitors (baricitinib, ruloxitinib)
   15. Mesenchymal Stem (Stromal) Cells
   16. Release Active Antibodies to Human Interferon Gamma
   17. Statins
   18. Supplements
      a. Vitamin C & Quercetin
      b. Vitamin D
      c. Zinc
      d. Melatonin
      e. Probiotics
      f. DHA/Omega 3 fatty acid

C. NEW IMMUNOMODULATORS REVIEWED FOR THE 3RD VERSION
   1. Anticoagulants
   2. Antihistamines
   3. Beta Glucan
   4. H2 receptor Blockers (famotidine)
   5. Mycophenolate Mofetil
   6. Virgin Coconut Oil (lauric acid)

PATHOGEN-SPECIFIC IMMUNOMODULATORS

POLYCLONAL ANTIBODY BASED AGENTS

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

1) Intravenous Immunoglobulin (IVIG)
2) Convalescent Plasma
3) Hyperimmune Globulin

1. INTRAVENOUS IMMUNOGLOBULIN (IVIG)

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Introduction

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

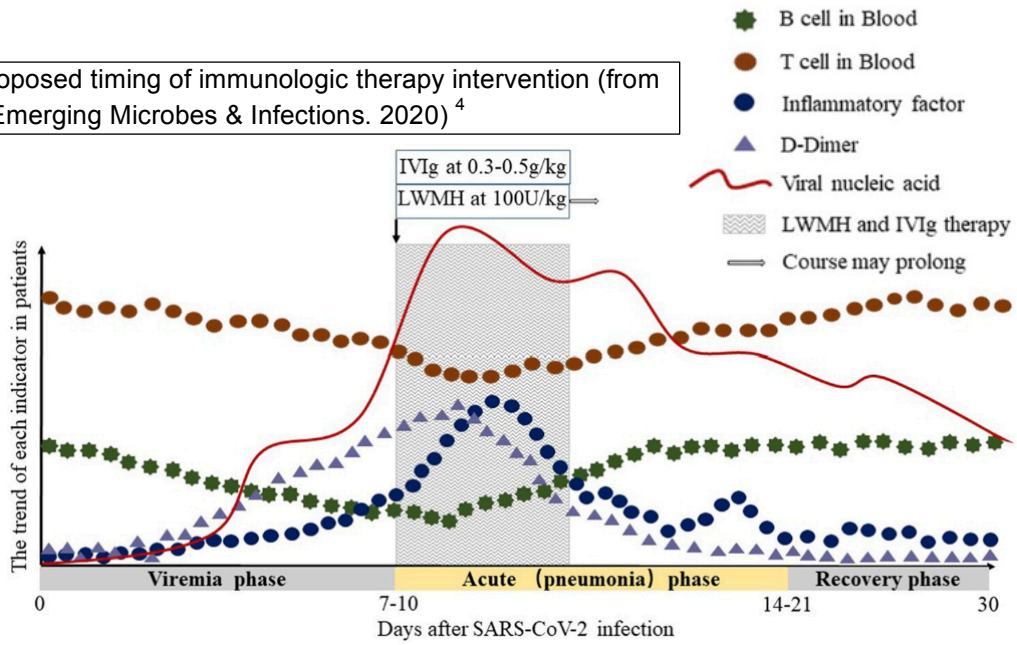
Mechanism of action and effect on COVID-19 infection

The mechanisms for its immunomodulatory effect are complex. These include modulation of antibody receptor expression and functions, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies, modulation of dendritic cell, T and B cell activation, differentiation, and effector functions. In vivo, a major mechanism by which IVIG exerts its anti-inflammatory effects is through the modulation of TH1 and TH2 cytokine and cytokine antagonist production.[2]

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

It is theorized that IVIG would be best given between day 7 to 14 or during the acute (pneumonia) phase to enhance the immune system (Figure 2)[4] and inhibit the formation of cytokine storm.[5] It is during this critical period that the immune system could be overwhelmed and pushed to a severe disease progression.

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



Efficacy Studies of IVIG in COVID-19 Infections (Appendix 3)

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]

As of August 16, 2020, there have been 32 case reports, and 12 case series done on IVIG. There are 7 randomized controlled trials listed on clinicaltrials.gov. Three of these researches are recruiting already, the other 4 have not yet started.

Dose and Timing of Administration

1. IV Immunoglobulin (IVIG) for is given as adjunctive treatment in COVID-19 patients at the first sign of respiratory deterioration:
    a. Dyspnea; or
    b. RR > 30/min; or
    c. SpO2 < 93%; or
    d. PaO2/FiO2 < 300; or
    e. Progression of lung infiltrates > 50% within 24-48 hours.[14]
2. Suggested IVIG dose is: 0.3-0.5 g/kg/day for 5 consecutive days. Start infusion at 30 ml/hr (0.5 ml/kg/hr), doubling rate every 15 minutes up to a maximum rate of 100 ml/hr. Consider rate and dose adjustments based on renal and cardiac status.[14]

Adverse Reactions

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

The majority of these symptoms are associated with rapid infusion and develop during the initial period of infusion which may be addressed by slowing down or stopping the infusion. Premedication is not a requirement for IVIG infusion; however, in some patients, acetaminophen, diphenhydramine or alternatively a non-sedating antihistamine and/or hydrocortisone one hour before the infusion may be given. Patients at increased risk of thromboembolic complications, or who have had prior thromboembolic complications, may benefit from additional preventive measures including pre-infusion hydration, low molecular weight heparin and use of low osmolality products. Rarely, acute kidney injury may occur with sucrose-containing products and careful evaluation and monitoring of renal function maybe necessary.[15] Routine serum IgA level testing in individuals without specific risk factor for IgA deficiency is not recommended. Importantly, IgA deficiency is not a contraindication to IVIG administration.[16-17]

Conclusion:

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

REFERENCES:

1. De Ranieri D. Intravenous immunoglobulin and its clinical applications. *Pediatr Ann*. 2017; 46:e6-7.
2. Negi V-S, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol*. 2007; 27:233-45.
3. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virol Sin*. 2020 [cited 2020 Mar 29]; Available from: https://link.springer.com/1-.1007/s12250-020-00207-4.
4. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection --- a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect*. 2020; 1-14.
5. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect.* 2020; 9(1):687-690. doi: https://doi.org/10.1080/22221751.2020.1741327.
6. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. Open Forum Infect Dis [Internet]. 2020 [cited 2020 Mar 29]; Available from: https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofaa102/5810740.
7. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J. 2020; ehaa190.
8. LeVine S, Dhaka GP, Penjor T, et al. Case report: the first case of novel coronavirus disease (COVID-19) in Bhutan. Am J Trop Med Hyg. 2020; 102:1205-1207. doi: https://doi.org/10.4269/ajtmh.20-0259.
9. Shi H, Zhou C, He P, et al. Successful treatment of plasma exchange followed by intravenous immunogloblin in a critically ill patient with 2019 novel coronavirus infection. Int J Antimicrob Agents. 2020; 56:105974. doi: https://doi.org/10.1016/j.ijantimicag.2020.105974.
10. Zhao K, Huang J, Dai D, et al. Acute myelitis after SARS-CoV-2 infection: a case report. *medRxiv preprint.* 2020. doi: https://doi.org/10.1101/2020.03.16.20035105.
11. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: a multi-center retrospective cohort study. *medRxiv preprint*. 2020. doi: https://doi.org/10.1101/2020.04.11.20061739.
12. Xie Y, Cao S, Dong H, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. *J Infect.* 2020; 81:318-356. doi: https://doi.org/10.1016/j.jinf.2020.03.044.
13. Zhou ZG, Xie SM, Zhang J, et al. Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses COVID-19 patients who have failed low-dose therapy. *Preprints* 2020, 2020030065. doi: https://doi.org/10.20944/preprints202003.0065.v1.
14. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patient with Coronavirus Disease 2019. *Open Forum Infect Dis*. 2020 [cited 2020 March 29]; Available from: https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofaa102/581-740.
15. Perez EE, Shehata N. Intravenous immune globulin: adverse effects. [cited 2020 March 29]; Available from: https://www.uptodate.com/contents/intravenous-immune-globulin-adverse-effects?source=mostViewed_widget.
16. Dantal J. Intravenous immunoglobulins: in-depth review of excipients and acute kidney injury risk. *Am J Nephrol*. 2013;38:275-84.
17. Stiehm ER. Adverse effect of human immunoglobulin therapy. *Transfus Med Rev*. 2013;27:171.

2. CONVALESCENT PLASMA

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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 are 2 completed case series on the use of convalescent plasma. In a pilot study by Duan et al., each patient

with severe COVID-19 received one dose (200 ml) of convalescent plasma with neutralizing antibody titers at or exceeding a 1:640 dilution between day 11 to day 20 from onset of symptoms. All 10 patients had improvement in symptoms (e.g. fever, cough, shortness of breath and chest pain) within 3 days of transfusion and demonstrated radiological improvement in pulmonary lesions. The study revealed that CP could significantly increase of maintain the neutralizing antibodies at high levels leading to the disappearance of viremia in 7 days. They compared these patients with a historical control group and found significant difference in clinical outcomes ($p<0.001$).[6] In this study all 10 patients on CP also received antivirals with 2 patients on interferon-a. Six patients also received methylprednisolone.

In a 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. All 5 patients also received antivirals and methylprednisolone.[7]

The first living update of a systematic review of convalescent plasma or hyper-immune immunoglobulin for people with COVID-19 was published last July 2020 in Cochrane Database. There were 20 completed studies (1 RCT, 3 controlled non-randomized studies of intervention (NRSIs), 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma. There are 98 ongoing studies, of which 50 are randomized. Overall risk of bias was high because of the study design, severity of disease of the participants and concurrent treatments. Their primary outcome was all-cause mortality and time to death. They could not analyze the results from the RCTs because not all participants had been discharged at the end of their follow-up. For the time to death, those in the convalescent plasma group may be prolonged but the evidence is very uncertain.[8] Piechotta et al. concluded that it is uncertain whether convalescent plasma from patients who recovered from COVID-19 is an effective treatment for people hospitalized with COVID-19. Authors also stated that it is very uncertain whether or not convalescent plasma have an impact on the number of severe complications. It has yet to be determined how much is actually related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma.

Other interventional trials in several countries are currently being conducted. (Appendix 4)

Recommended Dose

The appropriate volume for transfusion has not yet been determined. Based on previous pandemics and expert opinion, a volume from 200 to 600 ml (to 8 to 10 ml/kg,

with a maximum of 600 ml) once per day and up to three consecutive days has been suggested. [8,9,10]

Improvement of clinical signs & symptoms and decrease in values of clinical markers of inflammation were seen when plasma transfusion was started anywhere from day 10-day 22.[6,7]

A more restricted recommendation comes from the Italian Society of Transfusion Medicine and Immunohematology (SIMTI) and Italian Society of Hemapheresis and cell Manipulation (SidEM), that states that the optimal period to give immune plasma transfusion is within 7 days from the onset of symptoms as this coincides with peak of viremia within first week.[8] At the same time, there is evidence that giving it within the first 2 weeks may still be beneficial. Administration of immune plasma beyond 3 weeks from the onset of the disease seem to render it ineffective.[9]

Adverse Effects

There can be mild reactions like evanescent red spots as reported by Duan et al.[6] Other non-infectious hazards of tranfusions are allergic transfusion reactions and transfusion associated circulatory overload (TACO).[8] The risk for these adverse effects are likely to be no different from those of standard plasm transfusion. However, it may carry some risk of transfusion related acute lung injury (TRALI)[11] considering its use in active treatment of individuals with pulmonary disease. The specific risk of transfusion-transmitted SARS-CoV-2 is highly unlikely if one considers that only 1% of symptomatic patients have been reported to have detectable SARS-CoV-2 RNA in their blood and only asymptomatic plasma donors are recruited. Since there is yet no proof of COVID-19 infection via blood transfusion, its significance is largely theoretical.

There is a theoretical possibility of antibody-dependent enhancement (ADE) following transfusion of human anti-SARS-CoV-2 plasma.[12] ADE refers to a process whereby there is enhancement of disease in the presence of antibodies to a different strain of the virus causing the disease. As there is more than one strain of SARS-CoV-2 that have been identified, occurrence of this phenomenon has been offered as a possible reason for the geographic variation in disease severity

Conclusion:

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

REFERENCES:

1. Burton DR. Antibodies, viruses and vaccines. Nat Rev Immunol. 2002; 2:706–713.
2. Janeway CA, Travers P, Walport M, Shlomchik M (eds). Immunobiology. Fifth ed. New York: Garland Publishing; 2001.
3. Marasco WA, Sui J. The growth and potential of human antiviral monoclonal antibody therapeutics. Nat Biotechnol. 2007; 25: 1421–1434.
4. Reading SA, Dimmock NJ. Neutralization of animal virus infectivity by antibody. Arch Virol. 2007; 152:1047–1059.
5. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020; 395:565-574. doi: 10.1016/ S0140-6736(20)30251-8.
6. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A. 2020; 117:9490-9496. doi: 10.1073/pnas.2004168117.
7. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020; 323:1582-1589. doi: 10.1001/jama.2020.4783. [Epub ahead of print].
8. Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews, Issue7. Art. No.:CD013600.DOI: 10.1002/14651858.CD013600.pub2.
9. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020; 130:2757-2765. doi: 10.1172/JCI138745.
10. Accorsi P, Berti P, de Angelis V, et al. “osition paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. Blood Transfus. 2020; 18:163-166. doi: https://dx.doi.org/10.2450%2F2020.0124-20.
11. US Food and Drug Administration. Recommendations for investigational COVID-19 convalescent plasma. Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed on March 30, 2020.
12. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med. 2007; 176(9): 886–891.
13. Wan Y, Shang J, Sun S, et al. Molecular mechanism for anti-body-dependent enhancement of coronavirus entry. J Virol. 2020; 94(5): e02015-19.

3. HYPERIMMUNE GLOBULIN

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Introduction

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

Mechanism of Action

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

Clinical Studies

At present, not enough evidence on actual COVID-19 patients can be cited as to the efficacy and safety of using hyperimmune globulin. Piechotta et al. in a Cochrane systematic review[2] did not find completed studies on any of the ff:
Convalescent plasma therapy versus hyperimmune immunoglobulin, hyperimmune immunoglobulin versus standard care or placebo or hyperimmune immunoglobulin versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir).

Among those in the pipeline is an RCT from Iran listed as IRCT20200310046736N1 on plasma derived immunoglobulin-enriched solution (PDIES), produced by an improved Cohn method.

Another study listed as ClinicalTrials.gov/show/NCT04383548 aims to study the efficacy and safety of anti-SARS-CoV-2 hyper-immunoglobulins prepared from COVID-19 convalescent plasma using VIPS Mini-Pool IVIG medical device. The system is describe to potentially reduce the cost of production.

Recommended Dose

No reference studies available.

Adverse Effects

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

Availability

Several pharmaceutical companies are eyeing its development:

Takeda Pharmaceutical Company Limited (TSE:4502/NYSE: TAK) announced early in March the company's plan to develop a plasma-derived therapy for anti-Severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) polyclonal hyperimmune globulin (H-IG), TAK-888, to treat high-risk individuals with COVID-19.[3]

Emergent BioSolutions (NYSE:EBS) is also developing plasma-based treatments for COVID-19, including COVID-HIG, which will be derived from recovered patients, and COVID-EIG, made from plasma taken from horses that were given the virus.[4]

Giga Gen, Inc., based in California, USA, created recombinant hyperimmune globulin, that offers 100-fold higher potency than convalescent serum therapy. Hyperimmune globulins are derived from human donor B cells and are produced recombinantly at large scale in mammalian cells. The product called GIGA-2050 is a mix of 12,500 different antibody sequences selected from 16 exceptional responders to COVID-19. They are slated for the first human trials in early 2021[5]

Other companies joining the race to produce other hyperimmune globulin preparations include Regeneron, Astra Zeneca, Eli Lilly, and GSK.

Conclusion

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

REFERENCES:

1. Zhang Z, Xie YW, Hong J, et al. Purification of severe acute respiratory syndrome hyperimmune globulins for intravenous injection from convalescent plasma. Transfusion. 2005; 45(7):1160-4.
2. Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600.pub2.
3. Hopkins JS. Drugmaker Takeda is working on coronavirus drug. Wall Street Journal. Published March 4, 2020. Available from: https://www.wsj.com/articles/drugmaker-takeda-is-working-on-coronavirus-drug-11583301660. Accessed March 10, 2020.
4. Emergent BioSolutions. Emergent BioSolutions Partners with U.S. Government for Comprehensive Response to Expedite Development of Plasma-Derived Therapy for COVID-19. GlobeNewswire. Published April 02, 2020. Available from: https://www.globenewswire.com/news-release/2020/04/02/2011095/0/en/Emergent-BioSolutions-Partners-with-U-S-Government-for-Comprehensive-Response-to-Expedite-Development-of-Plasma-Derived-Therapy-for-COVID-19.html.
5. Keating SM, Mizrahi RA, Adams MS, et al. Capturing and Recreating Diverse Antibody Repertoires as Multivalent Recombinant Polyclonal Antibody Drugs. bioRxiv 2020. doi: 10.1101/2020.08.05.232975.

NON-PATHOGEN-SPECIFIC IMMUNOMODULATORS

1. ACE INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

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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 3). 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]

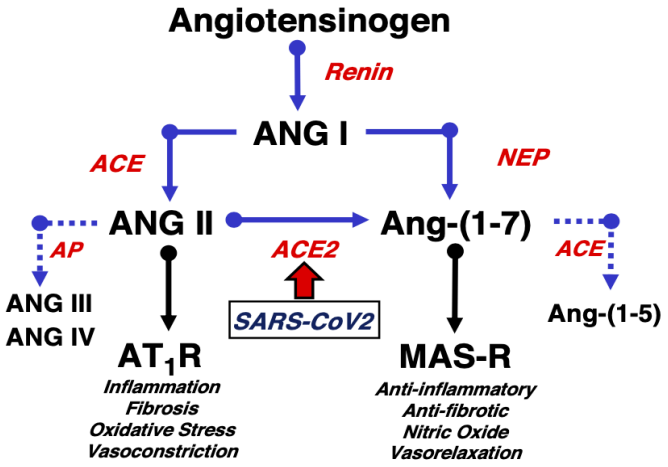

Figure 3. Processing and Functional scheme of the Renin-Angiotensin system [4]

Effect on COVID-19

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

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

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

Clinical Studies

Studies are ongoing on the benefits vs the risks in the utilization of ACEI/ARB among patients with cardiovascular disorders infected with COVID-19. (Appendix 5)

Recommended Dose[11]

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

Adverse Effects: [9]

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

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

Conclusion

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

REFERENCES:

1. Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. JAMA Cardiol 2020 April 23. Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2764299. Accesses May 12, 2020
2. Cheng H, Wang Y, Wang G-Q. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol 2020; 1– 5. Available from: https://doi.org/10.1002/jmv.25785
3. Sparks M, Crowley S, Coffman T. Classical Renin-Angiotensin System in Kidney Physiology. Compr Physiol 2014Jul 4930:1201-1228
4. Southfile://localhost/about/blank A Chappell M. COVID-19, ACE2, and the cardiovascular consequences Am J Physiol Heart Circ Physiol 318: H1084 –H1090, 2020. 13 APR 2020 https://doi.org/10.1152/ajpheart.00217.2020
5. Vaduganathan M, Vardeny O, Michel T, et al. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020; 382:1653-1659.
6. Paul M, Poyan MA, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev 2006; 86:747-803.
7. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decadelong structural studies of SARS. J Virology 2020 April; Vol 94 Issue 7. Available from: https://jvi.asm.org/content/94/7/e00127-20
8. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacol Res 2017 November; 125: 31-38. Available from: https://doi.org/10.1016/j.phrs.2017.06.005
9. Available from: http://www.medicinenet.com
10. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19 [published online ahead of print, 2020 Apr 27]. Hypertens Res. 2020;1-7. doi:10.1038/s41440-020-0455-8]
11. Sriram, K. and Insel, P.A. (2020), Risks of ACE Inhibitor and ARB Usage in COVID- 19: Evaluating the Evidence. Clin. Pharmacol. Ther. doi:10.1002/cpt.1863
12. Available from: https://www.healio.com/cardiology/vascular- medicine/news/online/%7Bfe7f0842-aecb-417b-9ecf-3fe7e0ddd991%7D/cardiology-societies-recommend-patient
13. https://www.cdc.giv/coronavirus/2019-ncov/hcp/faq.html - Drugs-and Investigational-Therapies

2. ALPHA 1 ADRENERGIC RECEPTOR ANTAGONISTS

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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] (Appendix 5)

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.

REFERENCES:

1. Grisanti L., Perez D., Porter J. Modulation of Immune Cell Function by α_1-adrenergic receptor activation. Curr Top Membr 2011 April; 67: 113-138. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624728/pdf/nihms454482.pdf
2. Scanzano A, Cosnetino M. Adrenergic regulation of innate immunity: a review. Front Pharmacol 2015 August; Vol 6: 171. Available from: http://dx.doi.org/10.3389/fphar.2015.00171. Accessed on: 2020 April 24.
3. Elenkov IJ, Wilder RL, Chrousos GP, et al. The sympathetic nerve - an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000 Dec; 52(4): 595-638.
4. Calcagni and Elenkov. Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. Ann N Y Acad Sci. 2006 Jun; 1069: 62-76.
5. Bao JY, Huang Y, Wang F, et al. Expression of alpha-AR subtypes in T lymphocytes and role of the alpha-ARs in mediating modulation of T cell function. Neuroimmunomodulation 20017; 14(6): 344-53.
6. Lappin D, Whaley K. Adrenergic receptors on monocytes modulate complement component synthesis. Clin Exp Immunol 1982 Mar; 47(3): 606-12.
7. Takahashi HK, Iwagaki H, Tamura R, et al. Alpha1-Adrenergic receptor antagonists induce production of IL-18 and expression of ICAM-1 and CD40 in human monocytes. J Immunother 2005 Jan-Feb; 28(1): 40-3.
8. Maestroni GJ. Dendritic cell migration controlled by α1b-adrenergic receptors. Journal of Immunology 2000; 165: 6743–6744.
9. Staedtke V, Bai R-Y, Kim K, et al. Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. Nature 2018; 564: 273–277.
10. Dong J, Mrabet O, Moze E, et al. Lateralization and catecholaminergic neuroimmunomodulation: prazosin, an alpha1/alpha2-adrenergic receptor antagonist, suppresses interleukin-1 and increases interleukin-10 production induced by lipopolysaccharides. Neuroimmunomodulation 2002; 10: 163–168.
11. Sugino H, Futamura T, Mitsumoto Y, et al. Atypical antipsychotics suppress production of proinflammatory cytokines and up-regulate interleukin-10 in lipopolysaccharidetreated mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2009; 33: 303– 307.
12. Kintscher U, Kon D, Wakino S, et al. Doxazosin inhibits monocyte chemotactic protein 1-directed migration of human monocytes. Journal of Cardiovascular Pharmacology 2001; 37: 532–539.
13. Lappin D, Whaley K. Adrenergic receptors on monocytes modulate complement component synthesis. Clinical and Experimental Immunology 1982; 47: 606–612.
14. Konig M, Powell M, Staedtke V, et al. Targeting the catecholamine-cytokine axis to prevent SARS-CoV2 cytokine storm syndrome**.** MedRxiv 2020 April. Available from: https://www.medrxiv.org/content/10.1101/2020.04.02.20051565v2. Accessed on: 2020 April 24.
15. Johns Hopkins University. Prazosin to prevent COVID19 (Prevent –COVID Trial) (Prevent). www.clinicaltrials.gov accessed 2020 May 11
16. Alpha 1 adrenergic receptor antagonists. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548719/. Accessed on: 2020 April 26.

3. ANTIVIRALS

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Introduction

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

Antiviral agents have also been included in 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. FAVIPIRAVIR / T-705/ FAVIPIRA/ FAVILAVIR

Introduction

Favipiravir is approved for treatment of novel influenza on February 15, 2020 in China and is currently undergoing clinical trials in treating COVID-19.[2]

Since the last edition of this paper, a number of studies have emerged with promising results. 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.[3]

Clinical Trials

A preprint of a randomized open-label clinical trial comparing favipiravir and arbidol showed no significant difference between the 2 groups in terms of clinical recovery rate at 7 days from the beginning of treatment. For the secondary outcomes,

the time to fever and cough relief in the favipiravir group was significantly shorter than that in the Arbidol group (P<0.0001). One limitation of this study is the diagnosis of COVID-19 without virologic tests. As such, included patients may have pneumonia due to other pathogens.[4]

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) [5]

A phase 3 clinical trial in India involving 150 patients with mild to moderate COVID-19 demonstrated faster viral clearance in the favipiravir group compared to the control group (Hazard Ratio 1.367 [95%CI 0.944,1.979]; p=0.129). Moreover, there was 40% faster achievement of clinical cure at 3 days (HR 1.749 [95% CI 1.096, 2.792]; p=0.029). A statistically significant "clinical cure" at 69.8% in 4 days, versus the standard supportive care group (44.9%) was reported. Among patients who deteriorated and required O2 support, those receiving favipiravir had a longer median time of use of oxygen of 5 days (95%CI 1.0,6.0) vs 2 days (95% CI 1.0-4.0) for those who received standard care. Adverse events (AEs) were reported in 26 patients in the favipiravir treatment arm (35.6%) as compared to six patients in the control arm (8%) however, most AEs were mild to moderate and none led to drug discontinuation or dosing adjustments. This study is not yet published and has not undergone peer review.[6]

There are 43 ongoing registered studies on favipiravir for COVID-19, including pharmacokinetic studies and 1 study on its possible prophylactic use. (Appendix 6-A)

Recommended dose

1600 mg 2x a day on day 1, then 600 mg 2x a day on days 2 to day 14, was used in a Chinese open label control study using favipiravir for moderate COVID-19 patients [5]

1800 mg 2x a day on day 1, then 800 mg 2x a day on day 2 onwards for a maximum of 14 days, was used in Glenmark's phase 3 clinical trial of favipiravir in patients with mild to moderate COVID-19[6]

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. It is contraindicated for known or suspected pregnant women and lactating women [5, 7]

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.[8]

b. LOPINAVIR/RITONAVIR (LPV/r)

Introduction

A protease inhibitor used as an antiretroviral treatment in combination with other antiretroviral agents for HIV 1 in adults and pediatric patients.[9] The updated guidelines of the Infectious Disease Society of America (IDSA) and the National Institutes of Health (NIH) for the management of COVID-19 recommends the use of LPV/r in hospitalized patients only in the context of a clinical trial.[10, 11] The Surviving Sepsis Campaign (SSC) guideline suggests against the use of LPV/r in critically ill adults.[12] The WHO interim guidance, Australian and New Zealand Intensive Care Society (ANZICS) guideline and National Institute for Health and Care Excellence (NICE) guideline did not address the use of LPV/r in COVID-19.[13]

On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms. These interim trial results show that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care. Solidarity trial investigators will interrupt the trials with immediate effect. For each of the drugs, the interim results do not provide solid evidence of increased mortality. [14]

Mechanism of Action

Lopinavir has in vitro inhibitory activity against SARS-CoV. It also blocks a post entry step in the MERS-CoV replication cycle.[9,15] Ritonavir is used in combination with lopinavir to increase the half-life through the inhibition of cytochrome P450.[15] Protease inhibitors prevent cleavage of the viral polyproteins resulting in the formation of non-infectious viral particles.[2]

All protease inhibitors increase the release of Macrophage Inflammatory Protein 1α (MIP-1a) and Monocyte Chemotactic Protein-1 (MCP-1) that function to recruit cells of the innate immune system.[16]

Clinical Studies

In a randomized, open-label, multi-center study involving a total of 127 patients, there was no difference in the time to clinical improvement for patients with severe COVID-19 who received LPV/r and standard of care compared to standard of care alone, in the intention to treat analysis (clinical improvement hazard ratio 1.31; 95% CI 0.95 to 1.80).[17] A study correlating viral clearance and blood biochemical index of 94 discharged patients showed no significant difference on the average length of hospital stay nor PCR negative conversion times among adult COVID-19 patients treated with LPV/r-IFN-α (N=46) and ribavirin-LPV/r + IFN-α combination (N=21). This study though, had a small sample size.[18]

An exploratory randomized study done in China involving 86 patients showed that the mean time for positive-to-negative conversion were not statistically different in the LPV/r group, the arbidol group and the control group (p=0.981). There was no

statistically significant difference in the rates of conversion after 7 days, 14 days and 21 days.[19]

On June 30, 2020, the RECOVERY trial found no benefit with lopinavir-ritonavir in COVID-19 and stopped randomization to that arm. A total of 1596 patients were randomized to lopinavir-ritonavir and compared with 3376 patients randomized to usual care alone. At the start of the trial, 4% required invasive mechanical ventilation, 70% required oxygen alone, and 26% did not require any respiratory intervention. The Independent Data Monitoring Committee recommended unblinding of results to the investigators and they found no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir-ritonavir vs. 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91-1.18]; p=0.58). The results were consistent in different subgroups of patients. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay. They had difficulty administering the drug to the mechanically ventilated patients, so they could not make conclusions on its effectiveness in this group of patients.[20]

The AustralaSian COVID-19 Trial (ASCOT) also removed the hydroxychloroquine and lopinavir/ritonavir arms of the trial, following the statement issued by the WHO together with the RECOVERY trial.[21]

As of July 6, 2020, there are 41 registered clinical trials investigating LPV/r for its use in COVID-19 management, while 4 trials were terminated. (Appendix 6-B)

Recommended Dose

Adult dose: 400mg/100 mg twice a day for 10days[22] or 14 days[17].
Pediatric dose: 7-15kg: 12mg/3mg/kg; 15-14kg: 10mg/2.5mg/kg; >40kg: as adult dose as used in clinical trials for COVID-19.
Doses to be taken twice a day for 1–2 weeks.

Adverse Effects and Drug Interactions

Adverse events observed among patients taking LPV/r for COVID-19 were gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal discomfort.[17] It may also cause hepatotoxicity, pancreatitis & ECG abnormalities.

Drug interactions are common with LPV/r due to their inhibition of cytochrome P450 that may result in increased plasma concentrations of other co administered drugs, consequently, leading to the therapeutic and adverse effects as well. Drugs that are contraindicated for use with LPV/r include alpha-1 adrenergic agonists (alfuzosin, prazosin, tamsulosin), neuroactive drugs (midazolam, triazolam, phenobarbital, phenytoin, carbamazepine), drugs for cardiovascular conditions (amiodarone, bepridil, flecainide, propafenone, quinidine, dronedarone, sildenafil), cholesterol lowering agents (lomitapide, lovastatin, simvastatin), antimicrobials (rifampicin, itraconazole, ketoconazole, metronidazole, elbasvir/grazoprevir), antihistamine terfenadine & astemizole, fluticasone, colchicine, ergot derivatives, ethinyl estradiol/ norethindrone acetate.[23, 24]

c. OSELTAMIVIR

Introduction

Oseltamivir is a viral neuraminidase inhibitor used for the treatment and prophylaxis of Influenza A, H1N1 Influenza A and Influenza B for both the pediatric and the adult population.[25] 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.[26] In Egypt, Oseltamivir is included in their standard of care treatment for confirmed COVID-19 patients.[27]

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.[25] 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.[28]
However, recent in vitro studies showed oseltamivir to have no antiviral effect against COVID-19.[29, 30]

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.[31, 32] 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.[33]

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

As of this writing, there are 13 registered clinical trials involving oseltamivir in COVID-19, with 7 trials presently recruiting subjects. To date, preliminary results are not yet available for these clinical trials.

Recommended dose

300 mg PO per day for 10-14 days used in a clinical trial for COVID-19 in Bangkok[34] or 75 mg PO every 12 hours for 5-10 days[27] as used in Egypt's treatment guideline for COVID-19.

Adverse Effects

Oseltamivir adverse effects reported are nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children.[35]

d. REMDESIVIR/ RDV/ GS-5734

Introduction

It is an investigational drug with broad-spectrum activities against MERS and SARS in vitro and has been tested for Ebola.[36] It is currently being investigated in clinical trials and is also available through expanded access and compassionate use for certain patient populations.

The NIH updated their revised recommendation in the COVID-19 treatment guidelines on July 24, 2020 stating that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO (BI), and recommends its use for 5 days or until hospital discharge, whichever comes first (AI). However there is uncertainty regarding whether starting remdesivir confers clinical benefit in patients with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO.[11]

Mechanism of Action

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

As the SARS-CoV study stated that it is probable that viral replication leads to activation of the pro-inflammatory cytokines, decrease in viral replication may possibly modulate the production of pro-inflammatory cytokines.[1]

Clinical Trials

Remdesivir is included in the WHO SOLIDARITY Trial for the treatment of COVID-19. Phase III trials are underway to evaluate the efficacy and safety of remdesivir in patients with mild or moderate and severe COVID-19 respiratory disease.

A study analyzed data from 53 patients who were given remdesivir for compassionate use and it showed that 68% of patients had improvement in terms of oxygen support, 18 days after receiving the first dose [37]

In a randomized, double-blind multicenter placebo-controlled trial of 237 severe COVID-19 patients, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). However, the trial did not attain the predetermined sample size of 452 subjects because the outbreak of COVID-19 was brought under control. [38]

A preliminary report from The Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the NIAID indicated that patients who received remdesivir had a 31% faster time to recovery than those who received placebo. The median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group.[39] This study has been completed but final results are not yet available.

In a randomized, open-label, phase 3 trial of 397 COVID-19 patients, it evaluated the safety and efficacy of both 5-day and 10-day dosing durations of remdesivir in patients with severe COVID-19. Sixty-five percent (65%) of patients who received a 5-day course of remdesivir showed a clinical improvement at day 14. As a comparison, 54% of patients received a 10-day course. After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course. A post-hoc analysis in terms of oxygen support status showed 40% (10 of 25) in the 5-day group had died by day 14, as compared with 17% (7 of 41) in the 10-day group[40] With the lack of randomization and no placebo control, however, the magnitude of benefit cannot be determined.

A preliminary report from an open-label study, this time with a control group, evaluated the safety and efficacy of 5-day and 10-day dosing regimens of remdesivir, compared with standard of care alone, in patients with moderate COVID-19. Initial results of the study demonstrated that patients in the 5-day remdesivir treatment group were 65 percent more likely to have clinical improvement at Day 11 compared with those in the standard of care group (OR 1.65 [95% CI 1.09-2.48]; p=0.017). The odds of improvement in clinical status with the 10-day treatment course of remdesivir versus standard of care were also favorable, trending toward but not reaching statistical significance (OR 1.31 [95% CI 0.88-1.95]; p=0.18). No new safety signals were identified with remdesivir across either treatment group.[41] This study will still have to be submitted for publication.

As of July 27, 2020, there are 19 registered clinical studies on remdesivir, with 10 studies, currently recruiting patients. (Appendix 6-C)

Recommended dose

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

Pediatric doses of remdesivir are used in patients with Ebola.[2] No data for use in pediatric COVID-19 patients.

Adverse Effects

Common adverse events in COVID-19 patients were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. Adverse events were more common in patients receiving invasive ventilation. [37]

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%).[40]

e. RIBAVIRIN/RBV

Introduction

Ribavirin is a broad-spectrum antiviral drug that hinders viral replication and spread.[42] It is primarily used for Respiratory Syncitial Viral infection, Influenza virus and chronic Hepatitis C.[1, 36] A study on patients with SARS treated with LPV/r and ribavirin had a lower risk of ARDS and death compared with monotherapy.[43] Most published international recommendation guidelines for the treatment of COVID-19 have not included ribavirin in their reports on treatment for COVID-19.[13]

Mechanism of Action

In a review of nucleotide inhibitors, RBV was found to cause human Coronavirus eradication in vitro.[44] For SARS patients, it is effective as prophylaxis and as treatment when combined with IFN-b.[45] Ribavirin has also been found to reduce macrophage activation, diminish Th2 cytokine production and preserve Th1 cytokine production among patients with hepatitis C virus.[46]

Clinical Trials

Ribavirin is presently included in the general treatment of COVID-19 in Chinese treatment guidelines[22]

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.[18]

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.[47]

There are 5 registered clinical trials, with 2 of which are currently recruiting. (Appendix 6-D)

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.[22]

Adverse Effects

Ribavirin can reduce hemoglobin concentration.[1] It is contraindicated in patients with severe hepatic and renal impairment and in known or suspected pregnant women.[48]

f. 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.[49]
China has added Umifenovir as an antiviral option in their treatment protocol for COVID-19.[50]

Mechanism of Action

Umifenovir has also been reported to produce an immunomodulatory response by inducing interferon production and stimulating the phagocytic function of macrophages.[43] Umifenovir prevents the fusion of the viral membrane with the endosome after endocytosis.[49]

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.[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.[51] The limitation of the said meta-analysis was the low quality and certainty of evidence and heterogeneity of the studies included. However, several ongoing clinical trials evaluating efficacy of umifenovir for COVID-19 may clarify this issue.

At the time of writing, there are a total of 14 ongoing registered clinical study for umifenovir in COVID-19 patients. One study in China involving 86 COVID patients was completed, with official results still to be published. (Appendix 6-E)

Recommended dose

200mg PO, 3 times a day, for not more than 10 days.[22]
Pedia: 10 mg/kg/d tid for <50 kg; 0.6 g/d tid for ≥50 kg[32]

An in vitro study suggested that umifenovir is potentially effective to treat COVID-19 patients, however the current recommended dose by the Chinese Guidelines may not be able to achieve the ideal therapeutic efficacy to inhibit SARS-CoV2 infection and should be increased.[30]

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.[52] 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.[49]

CONCLUSION FOR THE SIX ANTIVIRALS DISCUSSED

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

Even with the increasing number of published studies, convincing evidence of significant benefit does not exist yet for any antiviral treatment. Different countries may have adapted their own treatment guidelines; nonetheless, a unified recommendation for the use of any antiviral medication is still needed.

REFERENCES:

1. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral Remdesivir (GS-5734) Is mediated by the viral polymerase and the proofreading exoribonuclease. mBio 2018; 9(2): e00221-18. doi: 10.1128/mBio.00221-18. Accessed on April 5, 2020.
2. National Center for Biotechnology Information. PubChem Database. Ritonavir, CID=392622. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Ritonavir. Accessed on April 7, 2020.
3. Shannon A, Selisko B, Le NTT, et al. Favipiravir strikes the SARS-CoV-2 at its Achilles heel, the RNA polymerase. bioRxiv. Preprint 2020. doi: 10.1101/2020.05.15.098731.
4. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. MedRxiv 2020. doi: 10.1101/2020.03.17.20037432.
5. Cai Q, Yang M, Liu D, et al, Experimental treatment with Favipiravir for COVID-19: an open-label control study. Engineering 2020. doi: 10.1016/j.eng.2020.03.007.
6. Glenmark Pharmaceuticals Ltd. Glenmark announces top-line resutls from phase 3 clinical trial of Favipiravir in Patients with Mild to Moderate COVID-19. Available from: http://pdf.reuters.com/pdfnews/pdfnews.asp?i=43059c3bf0e37541&u=urn:newsml:reuters.com:20200722:nBSE5Jz1Pj . Accessed on July 23, 2020
7. Taisho Toyama Pharmaceutical Co., Ltd. Avigan. Available from: https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw. Accessed April 6, 2020.
8. Du YX, Chen XP. Favipiravir: Pharmacokinetics and concerns about clinical trials for 2019-nCoV infection. Clin Pharmacol Ther. 2020; 108(2):242-247. doi: 10.1002/cpt.1844.
9. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12(4): E372. doi: 10.3390/v12040372.
10. Bhimraj A, Morgan R, Schumaker A, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Available from: https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v1.0.4.pdf. Accessed on April 29, 2020.
11. National Institutes of Health. Covid-19 treatment guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov. Accessed July 24,2020
12. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020; 46:854-887. doi: 10.1007/s00134-020-06022-5.
13. Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence based guideline. CMAJ 2020; 192:E536-E545. doi: 10.1503/cmaj.200648.
14. World Health Organization. “Solidarity” clinical trial for COVID-19 treatments. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed on July 6, 2020.
15. Yao TT, Qian JD, Zhu WY, et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. J Med Virol. 2020;10. Available from: https://doi:10.1002/jmv.25729. Accessed 04/05/2020.
16. Malizia AP, Vioreanu MH, Doran PP, et al. HIV1 protease inhibitors selectively induce inflammatory chemokine expression in primary human osteoblasts. Antiviral Res. *2007;* 74(1):72–76. doi: 10.1016/j.antiviral.2006.12.003.
17. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020; 382:1787-1799. doi: 10.1056/NEJMoa2001282.
18. Yuan J, Zou R, Zeng L, et al. The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients. Inflamm Res. 2020: 69:599-606. doi: 10.1007/s00011-020-01342-0.
19. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Med (N. Y.). 2020; doi: 10.1016/j.medj.2020.04.001 [Epub ahead of print]
20. University of Oxford. No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY. Available from: https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery. Accessed on 29 August 2020.

21. ASCOT Trial. AustralaSian COVID-19 Trial (ASCOT) removes hydroxychloroquine and lopinavir/ritonavir arms of the trial. Available from: https://www.ascot-trial.edu.au/blogs/news/australasian-covid-19-trial-ascot-removes-hydroxychloroquine-and-lopinavir-ritonavir-arms-of-the-trial. Accessed on 29 August 2020.
22. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020; 14(1):58–60. doi: 10.5582/ddt.2020.01012.
23. HIV InSite UCSF Database of Antiretroviral Drug Interactions. All interactions with lopinavir/ ritonavir. Available from: http://arv.ucsf.edu/insite?page=ar-00-02&param=3&post=4. Accessed May 19, 2020.
24. Dorward J, Gbinigie K. Lopinavir/ritonavir: a rapid review of effectiveness in COVID-19. April 14, 2020 Available from: https://www.cebm.net/covid-19/lopinavir-ritonavir-a-rapid-review-of-the-evidence-for-effectiveness-in-treating-covid/. Accessed May 19, 2020.
25. National Center for Biotechnology Information. PubChem Database. Oseltamivir. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Oseltamivir. Accessed April 28, 2020.
26. Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020; 10.1001/jama.2020.6019. doi: 10.1001/jama.2020.6019.
27. Tobaiqy M, Qashqary M, Al-Dahery S, et al. Therapeutic management of COVID-19 patients: a systematic review, Infection Prevention in Practice 2020; 100061. doi: 10.1016/j.infpip.2020.100061.
28. Muralidharan N, Sakthivel R, Velmurugan D, et al. Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19 [published online ahead of print, 2020 Apr 16]. J Biomol Struct Dyn. 2020;1-6. doi: 10.1080/07391102.2020.1752802.
29. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020;178:104786. doi: 10.1016/j.antiviral.2020.104786.
30. Wang X, Cao R, Zhang H, et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov. 2020; 6:28. doi: 10.1038/s41421-020-0169-8.
31. Yin W, Mao C, Luan X, et al. Structural basis for inhibition of the RNA dependent RNA polymerase from SARS-Cov-2 by Remdesivir. Science. 2020: eabc1560 doi: 10.1126/science.abc1560.
32. Peng H, Gao P, Xu Q, et al. Coronavirus disease 2019 in children: characteristics, antimicrobial treatment, and outcomes. J Clin Virol. 2020;128:104425. doi:10.1016/j.jcv.2020.104425
33. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069. doi: 10.1001/jama.2020.1585
34. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Favipiravir, Protease Inhibitors, Oseltamivir -Gpo, Hydroxychloroquine for Treatment of COVID-19 (FIGHT-COVID-19). Available from: https://clinicaltrials.gov/ct2/show/NCT04303299?term=oseltamivir&cond=covid+19&draw=1&rank=1. Accessed April 28, 2020.
35. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2014;2014(4):CD008965. doi: 10.1002/14651858.CD008965.pub4.
36. Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020. doi: 10.1038/d41573-020-00016-0.
37. Grein J, Ohmagari N, Shin D, et al. Compassionate use of Remdesivir for patients with severe COVID-19. N Engl J Med. 2020; 382:2327-2336. doi: 10.1056/NEJMoa2007016.
38. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with sever COVID-19: a randomised double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395:P1569-1578. doi:10.1016/S0140-6736(20)31022-9.
39. National Institutes of Health. NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19. April 29, 2020. Available at: https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19. Accessed April 30, 2020.
40. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020; doi: 10.1056/NEJMoa2015301.

41. Gilead. Gilead Announces Results From Phase 3 Trial of Remdesivir in Patients With Moderate COVID-19. Available from: https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19. Accessed June 1, 2020.
42. Zhang C, Huang S, Zheng F, et al. Controversial treatments: an updated understanding of the Coronavirus Disease 2019. J Med Virol. 2020. doi: 10.1002/jmv.25788.
43. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004; 59(3):252–256. doi: 10.1136/thorax.2003.012658.
44. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020; 248:117477. doi: 10.1016/j.lfs.2020.117477.
45. Morgenstern B, Michaelis M, Baer PC, et al. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochem Biophys Res Commun. 2005; 326(4):905–908. doi: 10.1016/j.bbrc.2004.11.128.
46. Feld JJ, Lutchman GA, Heller T, et al. Ribavirin improves early responses to peginterferon through improved interferon signaling. Gastroenterology. 2010; 139(1):154–62.e4. doi: 10.1053/j.gastro.2010.03.037.
47. Hung IFN, Lung KC, Tso EYK, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020; 395:P1695-1704. doi: 10.1016/S0140-6736(20)31042-4.
48. National Center for Biotechnology Information. PubChem Database. Ribavirin. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/37542. Accessed April 10, 2020.
49. Blaising J, Polyak SJ, Pécheur EI. Arbidol as a broad-spectrum antiviral: an update. Antiviral Res. 2014; 107:84–94. doi: 10.1016/j.antiviral.2014.04.006.
50. Song Y, Zhang M, Yin L, et al. COVID-19 treatment: close to a cure? a rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents. 2020; 56(2):106080. doi: 10.1016/j.ijantimicag.2020.106080.
51. Huang D, Yu H, Wang T, et al. Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Med Virol. 2020;10.1002/jmv.26256. doi: 10.1002/jmv.26256.
52. Javorac D, Grahovac L, Manić L, et al. An overview of safety assessment of the medicines currently used in the treatment of COVID-19 disease. Food Chem Toxicol. 2020; 144:111639. doi: 10.1016/j.fct.2020.111639 Accessed 08/02/2020

4. ASPIRIN

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Introduction

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

Mechanism of Action

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

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

Clinical trials

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

Recommended Dose

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

Adverse Effect

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

Conclusion

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

REFERENCES

1. Huemer HP, Possible Immunosuppressive Effects of Drug Exposure and Environmental and Nutritional Effects on Infection and Vaccination. Hindawi Publishing Corporation Mediators of Inflammation 2015; Article ID 349176: 7 pages. Available from: https://www.hindawi.com/journals/mi/2015/349176/
2. Rumore M, Aron SM and Hiross EJ. A Review of Mechanism of Action of Aspirin and Its Potential as an Immunomodulating Agent. Medical Hypothesis 1987; Vol 22 Issue 4: 387-400.
3. https://clinicaltrials.gov/ct2/show/NCT04365309?term=Aspirin&cond=COVID&draw=2&rank=3. Accessed on 2020 April 28.
4. https://clinicaltrials.gov/ct2/show/NCT04363840?term=Aspirin&cond=COVID&draw=2&rank=1. Accessed on 2020 April 28
5. https://clinicaltrials.gov/ct2/show/record/NCT04343001?term=Aspirin&cond=COVID&draw=2&rank=2. Accessed on 2020 April 28
6. https://clinicaltrials.gov/ct2/show/NCT04368377?term=Aspirin&cond=COVID&draw=2&rank=4. Accessed on 2020 April 28
7. https://clinicaltrials.gov/ct2/show/NCT04333407?term=Aspirin&cond=COVID&draw=2&rank=5. Accessed on 2020 April 28
8. Anderson LA, Sinha S, Durbin K, ed. et al Aspirin side effects. Accessed from: https://www.drugs.com/sfx/aspirin-side-effects.html#refs. Accessed on 2020 May 1.

5. AZATHIOPRINE

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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.

REFERENCES:

1. Elion GB, Hitchings GH. Azathioprine. Handbook Exp Pharmacol 1975; 38:404.
2. Huskisson EC. Azathioprine. Clin Rheum Dis 1984; 10:325.
3. McKendry RJR. Purine analogues. In: Second Line Agents in the Treatment of Rheumatic Diseases, Dixon J, Furst BE (Eds), Marcel Decker, New York 1991.
4. Trotter JL, Rodey GE, Gebel HM. Azathioprine decreases suppressor T cells in patients with multiple sclerosis. N Engl J Med 1982; 306:365.
5. Bacon PA, Salmon M. Modes of action of second-line agents. Scand J Rheumatol Suppl 1987; 64:17.
6. Crilly A, McInnes IB, Capell HA, Madhok R. The effect of azathioprine on serum levels of interleukin 6 and soluble interleukin 2 receptor. Scand J Rheumatol 1994; 23:87.
7. Bacon PA, Salmon M. Modes of action of second-line agents. Scand J Rheumatol Suppl 1987; 64:17.
8. Pinals RS. Azathioprine in the treatment of chronic polyarthritis: longterm results and adverse effects in 25 patients. J Rheumatol 1976; 3:140.
9. Singh G, Fries JF, Spitz P, Williams CA. Toxic effects of azathioprine in rheumatoid arthritis. A national post-marketing perspective. Arthritis Rheum 1989; 32:837

6. AZITHROMYCIN

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Introduction

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

Mechanism of Action

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

Clinical Studies

In an open-label study of 36 patients with COVID-19, the use of azithromycin in combination with hydroxychloroquine (6/6) compared to hydroxychloroquine alone (7/14) appeared to be associated with a more rapid decline in viral RNA (p=0.05). At day 6 post- inclusion, all of the patients treated with hydroxychloroquine and azithromycin
combination were virologically cured.[4] The results this ongoing study should be interpreted with caution due to methodologic concerns and small sample size. (Appendix 7)

At present, there are 109 registered studies in clinicaltrials.gov using Azithromycin alone (1 ongoing trial) or in combination with other immunomodulators for COVID-19.

Adverse Effects

Reactions like QTc prolongation and ventricular arrhythmias, including torsades de pointes have been reported. Patients admitted with COVID-19 are likely to have longer baseline QTc and have higher potential arrhythmic risks especially in the background of a previous cardiac pathology (arrhythmias, heart failure, hypokalemia, hypomagnesemia)[5,6,7] QTc monitoring in this setting is essential to identify those who are at increased risk for torsades de pointes so aggressive countermeasures may be implemented.[6,8]

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.[6]

Conclusion

Currently, conflicting data regarding combination therapy from different studies all over the world are starting to come out. Though combination of azithromycin and hydroxychloroquine can decrease viral RNA load the addition of azithromycin may potentially trigger cardiovascular complications. There is one ongoing trial on the use of azithromycin alone in mild to moderate COVID-19.

REFERENCES

1. Giamerellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. Int J Antimicrob Agents 2008 Jan; 31(1): 12-20.
2. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev 2010; 23: 590-615. Available from: https://dx.doi.org/10.1128%2FCMR.00078-09
3. Parnham MJ, Haber VE, Giamarellos-Bourboulis EJ, et al. Azithromycin: Mechanisms of action and their relevance for clinical applications. Pharmacol Ther 2014 Aug; 143:225–245.
4. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949.
5. Gahart B, Nazareno A. Ortega M. Gahart's Intravenous Medications 2020. 36th edition; pp 154-155.
6. Philippine Pediatric Society and Pediatric Infectious Diseases Society of the Philippines. Interim Guidelines on the screening, assessment and clinical management of pediatric patients with suspected or confirmed coronavirus disease 2019 (CoViD-19) 2020 March 30. Available from: http://www.pidsphil.org. Accessed on 10 April 2020.
7. Lane, JCE, Weaver J, Kostka A, et al.. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid widespread use for COVID-19: a multinational, network cohort and self-controlled case series study. MedRxiv 2020. doi.org/10.1101/2020.04.08.20054551.
8. Simpson T, Kovacs R, Stecker E. Ventricular Arrhythmia Risk Due to Hydroxychloroquine - Azithromycin Treatment For COVID-19. Cardiology Magazine, American College of Cardiology 2020 April.

7. BCG VACCINE

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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.

REFERENCES:

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

8. CALCINEURIN INHIBITORS

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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

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

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

Mechanism of Action

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

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

Cyclosporine has been used to treat cytokine storm related syndromes in 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] As of September 20, 2020, there are 4 studies, in the recruiting stage, that propose to use Cyclosporine as intervention for COVID-19. (Appendix 8)

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]

REFERENCES:

1. Flores C, Fouquet G, Moura IC et al. Lessons to Learn From Low-Dose Cyclosporin-A: A New Approach for Unexpected Clinical Applications. Front. Immunol. 2019, 10, 588. https://doi.org/10.3389/fimmu.2019.00588. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2019.00588/full
2. Brunton LL, Hilal-Dandan R, BC Knollmann, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th Edition. New York: McGraw-Hill Education c2018. Chapter 35, Immunosuppressants and Tolerogens; p.640-642
3. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol [Internet] 2011 Nov; 92, 2542–2548 Available from: https://pubmed.ncbi.nlm.nih.gov/21752960/
4. Przybylski M, Dzieciątkowski T, Zduńczyk D et al (2010) Microbiological findings and treatment of EBV-associated hemophagocytic lymphohistiocytosis: a case report. Arch Immunol Ther Exp 58:247–252
5. Tsuda H, Shirono K.; Successful treatment of virus-associated haemophagocytic syndrome in adults by cyclosporin A supported by granulocyte colony-stimulating factor. Br J Haematol. 1996 Jun;93(3):572-5. doi: 10.1046/j.1365-2141.1996.d01-1707.x. PMID: 8652375
6. Bennett TD, Fluchel M, Hersh AO, et al. Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis Rheum 2012;64:4135–42. Available from: https://doi.org/10.1002/art.34661
7. Behrens EM, Koretzky GA. Review: Cytokine Storm Syndrome: Looking Toward the Precision Medicine Era. Arthritis Rheumatol.[Internet] 2017;69:1135–43 Available from: https://doi.org/10.1002/art.40071
8. Ning L, et Liu L, Li W, et al, Novel coronavirus (SARS-CoV-2) infection in a renal transplant recipient: Case report, Am J Transplant. 2020;00:1–5, Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15897
9. Sanchez-Pernaute O, Romero-Bueno FI, O'Callaghan AS, Why choose cyclosporin A as first-line therapy in COVID-19 pneumonia, Reumatologia Clinica (2020), doi: https://doi.org/10.1016/j.reuma.2020.03.001

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. (Appendix 8)

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. (Appendix 8)

Adverse Effects

Commonly seen adverse effects include the following: nephrotoxicity, neurotoxicity (e.g., tremors, headache, motor disturbances, seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes. As with other immunosuppressive agents, there is an increased risk of secondary tumors and opportunistic infections.[2]

Conclusion

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

REFERENCES:

1. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel Covid-19 – a systematic review of current evidence. Ecancermedicalscience [Internet] 2020;14:1022. Published: 27/03/2020 Available from: https://doi.org/10.3332/ecancer.2020.1022
2. Brunton LL, Hilal-Dandan R, BC Knollmann, editors. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th Edition. New York: McGraw-Hill Education c2018. Chapter 35, Immunosuppressants and Tolerogens; p.639-640.
3. Yoon KH. Efficacy and cytokine modulating effects of tacrolimus in systemic lupus erythematosus: a review. J Biomed Biotechnol [Internet]. 2010;2010: 686480 Published online 2010 Jun 28. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2896715/
4. Aoyama-Maeda N, Horino T, Ichii O, Terada Y. Macrophage activation syndrome associated with systemic lupus erythematosus treated successfully with the combination of steroid pulse, immunoglobulin and tacrolimus, Rom. J. Intern. Med 2018, 56,2, 117-121, Published online: 17 May 2018 Available from: https://doi.org/10.1515/rjim-2017-0043
5. Carbajo-Lozoya J, Müller MA, and Kallies S, et al (2012) Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506 Virus Res 165(1) 112–117 https://doi.org/10.1016/j.virusres.2012.02.002 PMID: 22349148
6. Carbajo-Lozoya J, Ma-Lauer Y, and Malesevic M, et al (2014) Human coronavirus NL63 replication is cyclophilin A-dependent and inhibited by non-immunosuppressive cyclosporine A-derivatives including Alisporivir Virus Res 184 44–53 https://doi.org/10.1016/j.virusres.2014.02.010 PMID: 24566223
7. Banerjee D, Popoola J, Shah S, et al. COVID-19 infection in kidney transplant recipients [e-pub ahead of print]. Kidney Int. 10.1016/j.kint.2020.03.018.
8. Bhoori S, Rossi RE, Citterio D et al, COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy, The Lancet Gastroenterology and Hepatology, Vol 5:6, p532-533 [Published ahead of print :April 09, 2020] Available from: :https://doi.org/10.1016/S2468-1253(20)30116-3
9. Willicombe M, Thomas D, McAdoo S. COVID-19 and Calcineurin Inhibitors: Should They Get Left Out in the Storm? Journal of the American Society of Nephrology [Internet] April 2020, Available from: https://jasn.asnjournals.org/content/early/2020/04/20/ASN.2020030348

9. COLCHICINE

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Introduction

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

Mechanism of Action

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

Clinical Studies

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

Recommended Dose

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

Adverse Reactions

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

Conclusion

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

REFERENCES:

1. Gültekin N, Kucukates E. Microtubule Inhibition Therapy by Colchicine in Severe Myocarditis Especially Caused by Epstein-Barr and Cytomegalovirus Co-infection During a Two-Year Period: A Novel Therapeutic Approach. The Am J Cardio 2015 March; 16(115):170.
2. Jawalant Raval, Nagaraja V, Eslick GD, et al. The Role of Colchicine in Pericarditis – A Systematic Review and Meta-analysis of Randomised Trials. Heart, Lung and Circulation 2015 July; 24(7): 660-666.
3. Roubille F, Kritikou E, Busseuil D, et.al. Colchicine: an old wine in a new bottle? Antiinflamm Antiallergy Agents Med Chem 2013; 12 (1): 14-23.
4. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020 Apr 20; 108427.
5. Jones HD, Crother TR, Gonzalez-Villalobos RA, et al. The NLRP3 inflammasome is required for the development of hypoxemia in LPS/mechanical ventilation acute lung injury. Am J Respir Cell Mol Biol 2014; 50 (2): 270-280.
6. Dolinay T, Kim YS, Howrylak J, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med 2012; 185 (11): 1225-1234.
7. Deftereos S, Siasos G, Giannopoulos G, et al. The Greek study in the effects of colchicines in CO-vid-19 complications, prevention (GRECCO-19 study): Rationale and study design. Hellenic J Cardiol 2020 April 3. Available from: https://doi.org/10.1016/j.hjc.2020.03.002

10. CORTICOSTEROIDS

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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

According to the WHO Interim Guidance dated March 13, 2020, systemic glucocorticoids should not be given routinely to treat viral pneumonia outside of clinical trials. This is due to the lack of evidence of effectiveness and possible harm.[6] The recommendation is based on previous a systematic review of observational studies on SARS where corticosteroids administered to patients with SARS provided no survival benefit and may pose possible harm. Early observational studies on COVID 19, however, showed a small improvement in mortality and faster resolution of shock with steroid use.[7]

The use of corticosteroids for COVID-19 patients as part of the clinical trials were first done in Wuhan, China where the first cases were observed.

One published retrospective observational study done in Wuhan Union Hospital looked at the effect of giving IV methylprednisolone 1-2 mg/kg per day to patients with severe COVID-19 pneumonia. Out of 46 patients, 26 received methylprednisolone in addition to standard of care. These patients had shorter duration of fever, faster improvement of SpO2 and better resolution of chest CT scan findings.[8]

In another observational study in First Hospital in Changsha, 10 COVID-19 patients were given low dose methylprednisolone plus 10 grams/day of IVIG aside from standard of care. But it was only when both the methylprednisolone and IVIG were increased to 160 mg/day and 20 grams/day, respectively, did they observe clinical improvement, PaO2/FiO2 and lymphocyte counts increased and decreased infiltrates on chest CT scan.[9]

The sample size for both of the above studies, however, were too small to draw proper conclusions and support the use of steroids in severe COVID-19 patients.

Currently, there are two ongoing studies that have released preliminary data showing favorable outcome on the use of steroids. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial which provided evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days decreased the incidence of death among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and those receiving oxygen support without mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not with those with no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).[10] The other ongoing study, GLUCOCOVID 63[11] is a multicentric, partially randomized, preference, open-label trial among adults with COVID-19 pneumonia. It involved administration of methylprednisolone (IV 40 mg q12 for 3 days the 20 mg q12 for 3 days). Preliminary reports showed reduction in the progression to severe respiratory insufficiency and ARDS among patients.

As of August 10, 2020 there have been nine additional studies on corticosteroids. Two randomized open label trials and one randomized triple blind study are investigating the use of inhaled corticosteroids either alone or in combination with an intranasal corticosteroid among patients with mild COVID-19.

Six studies (including the RECOVERY Trial and GLUCOCOVID 63) involve the use of systemic steroids as a short course treatment. One of these is an observational retrospective case control study on dexamethasone. It has been completed, but has not been published. Two randomized controlled trials are still in the recruitment phase. One involves the use of oral prednisone and the other methylprednisolone. Another randomized open label study looks into colchicine and prednisone versus standard of care in reducing mortality. (Appendix 9)

Recommended Dose

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

The RECOVERY Trial recommends the use of dexamethasone IV or oral at 6mg once per day for up to 10 days.[4410]

Adverse Effects

Patients must be closely monitored and issues on hyperglycemia and electrolyte imbalances should be addressed. One must also watch out for recurrence of inflammation, secondary infections, adrenal insufficiency and possibly drug-drug interactions.

Conclusion

The use of corticosteroids (particularly dexamethasone) as adjunctive treatment 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.

REFERENCES:

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb; 395 (10223): 497–506.
2. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol 2020 March; 214:108393. [Epub ahead of print]
3. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence. Ecancermedicalscience. 2020 Mar 27; 14:1022.
4. Favallia EG, Ingegnolia F, De Luciaa O, Cincinellib G. COVID-19 infection and rheumatoid arthritis: faraways, so close. Autoimmunity Reviews. 2020; 19: 102523.
5. Cron RQ, Behrens EM (editors). *Cytokine Storm Syndrome.* Cham, Switzerland: Springer International Publishing; 2019. 581-583.
6. World Health Organization Interim Guidance. Clinical management of severe acute respiratory infection when COVID-19 is suspected. WHO Reference Number WHO/2019-nCoV/Clinical/2020.4.
7. Doctors Try Steroids to Treat Coronavirus Patients, Against WHO Counsel. (Accessed on: 20 April 2020) Available from: https://www.wsj.com/articles/doctors-try-steroids-to-treat-coronavirus-patients-against-who-counsel-11584878400.
8. Wang Y, Jiang W, He Q, et al. Early, low-dose, short term application of corticosteroid treatment in patients with severe covid 19 pneumonia: A single center experience from Wuhan China. (Cited on 20 April 2020) Available from: https://www.researchgate.net/publication/339892221_Early_low-dose_and_short-term_application_of_corticosteroid_treatment_in_patients_with_severe_COVID-19_pneumonia_single-center_experience_from_Wuhan_China. (preprint).
9. Zhou Z, Xie S, Zhang J, et al. Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses COVID-19 patients who have failed low-dose therapy. *Preprints.* 2020. 2020030065 (Cited on 21 April 2020)
10. The Recovery Collaborative Group. Dexamethasone in hospitalized patients with COVID19---Preliminary report. New Engl J Med. Epub July 17, 2020. Available from https://www.nejm.org/doi/10.1056/. Last accessed August 9, 2020.
11. Corral-Gudino L. Bahamonde A, delas Revillas FA, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. medRxiv preprint posted June 18, 2020. Available from https://doi.org/10.1101/2020.06.17.20133579. Last Accessed August 9, 2020.

11. HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (CQ)

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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.(Appendix 10)

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.

REFERENCES:

1. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in prevention infection and progression. J Antimicro Chemother 2020; 75:1667-1670.
2. Devaux CA, Rolain JM, Colson P. and Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. Int J Antimicrob Agents 2020; 55(5):105938.
3. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005; 2:69. Google Scholar Crossref PubMed
4. Yang ZY, Huang Y, Ganesh L, et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced dentritic cell transfer through DC-SIGN. J Virol. 2004; 78(11); 5642-50.
5. Savarino A, Mothanje B, Rastrelli E, et al. Anti HIV effects of chloroquine: inhibition of viral particle glycosylation and synergism with protease inhibitors. JAIDS 2001; 35(3):223-232.
6. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol 2020; 16(3):155-166. doi: 10.1038/241584-020-0372-x.
7. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv 2020. doi: https://doi.org/10.1101/2020.03.22.20040758.
8. Chen J, Liu D, Liu L, et al. (2020) A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Que Ban 2020; 49(2):215-219.
9. Mahévas M, Tran V, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv 2020. doi: 10.1101/2020.04.10.20060699.
10. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 2020; 382(25):2411-2418.
11. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 2020; 3(4):e208857.
12. World Health Organization. WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. Available from: https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19
13. https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19. Accessed on August 13 , 2020.
14. Siemieniuk RAC, Bartoszko JJ, Ge L, et.al. Drug treatments for COVID-19: living systematic review and network meta-analysis. BMJ 2020; 370:m2980. doi: https://doi.org/10.1136/bmj.m2980.
15. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med 2020; 383:517-525. doi: 10.1056/NEJMoa2016638
16. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020: 56(1):105949. doi:10.1016/j.ijantimicag.2020.105949

17. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Travel Med Infect Dis 2020; 34:101663. doi: 10.1016/j.tmaid.2020.101663.
18. Molina JM, Delaugerre C, Goff JL, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Méd Mal Infect. 2020; 50(4):384. doi:10.1016/j.medmal.2020.03.006
19. Cavalcanti A, Zampieri F, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild to moderate COVID-19. New Engl J Med 2020. doi:10.1056/NEJMoa2019014.
20. National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). China National Health Commission, 2020. Available from: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. Accessed on September 5, 2020.
21. Italian Society of Infectious and Tropical Diseases. Guideline for the treatment of people with COVID-19 disease (2nd ed). 2020. Available from: https://www.acep.org/globalassets/images/italian-guidelines-for-covid-19-google-translate.pdf.pdf. Accessed on September 5, 2020.
22. Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium. Available from: https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf. Accessed September 5, 2020.
23. Gangopadhyay KK, Sinha B, Ghosal, S. Compliance of the Indian National Task Forces guidelines for COVID-19 recommendation by Indian doctors – A survey. Diabetes Metab Syndr 2020; 14(5):1413-1418. doi: 10.1016/j.dsx.2020.07.040
24. Chorin E, Matthew D, Shulman E, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. medRxiv 2020. doi: doi: https://doi.org/10.1101/2020.04.02.20047050.

12. INOSINE PRANOBEX

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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.

REFERENCES:

1. Sliva J, Pantzartzi C, Votava M. Inosine Pranobex: A key player in the game against a wide range o viral infections and non-infectious diseases.Adv Ther.2019;36(8):1878-1905.
2. Petrova M, Jelev D, Ivanova A, Krastev Z. Isoprinosine affects serum cytokine levels in healthy adults. J Interferon Cytokine Res. 2010;30(4):223–228. Available from https://pubmed.ncbi.nlm.nih.gov/20038210/. Accesses 22 April 2020
3. Lasek W, Janyst M, Wolny R, Zapala L, Bocian K, Drela N. Immunomodulatory effects of inosine pranobex on cytokine production by human lymphocytes. Acta Pharm. 2015;65(2):171–180. Available from https://content.sciendo.com/view/journals/acph/65/2/article-p171.xml. Accessed 22 April 2020
4. Milano S, Dieli M, Millott S, Miceli MD, Maltese E, Cillari E. Effect of isoprinosine on IL-2, IFN-gamma and IL-4 production in vivo and in vitro. Int J Immunopharmacol. 1991;13(7):1013–1018. Available from https://www.sciencedirect.com/science/article/pii/019205619190055C?via%3Dihub. Accessed 22 April 2020
5. Tsang KY, Pan JF, Swanger DL, Fudenberg HH. In vitro restoration of immune responses in aging humans by isoprinosine. Int J Immunopharmacol. 1985; 7(2): 199–206.
6. Tsang KY, Fudenberg HH, Pan JF, Gnagy MJ, Bristow CB. An in vitro study on the effects of isoprinosine on immune responses in cancer patients. Int J Immunopharmacol. 1983;5(6):481–490. Available from https://www.sciencedirect.com/science/article/pii/0192056183900413?via%3Dihub. Accessed 23 April 2020
7. Ohnishi H, Kosuzume H, Inaba H, Okura M, Morita Y, Mochizuki H, et al. Mechanism of host defense suppression induced by viral infection: mode of action of inosiplex as an antiviral agent. Infect Immun.1982;38(1):243–250.Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC347725/pdf/iai00145-0253.pdf. Accessed 23 April 2020
8. Renoux G, Renoux M, Guillaumin J-M. Isoprinosine as an immunopotentiator. J Immunopharmacol. 1979;1(3):337–356.
9. Campoli-Richards DM, Sorkin EM, Heel RC. Inosine pranobex. Drugs. 1986;32(5):383–424.
10. Beran J, Salapova E, Spajdel M. Inosine pranobex is safe and effective for the treatment of subjects with confirmed acute respiratory viral infections: analysis and subgroup analysis from a Phase 4, randomized, placebo-controlled, double-blind study.BMC Infect Dis.2016; 16:648.
11. Brzeski M, Madhok R, Hunter JA, Capel HA. Randomised, double blind, placebo-controlled trial of inosine pranobex in rheumatoid arthritis. Ann Rheum Dis. 1990;49:293–295.
12. Majewska A, Lasek W, Janyst M, Mlynarczyk G. In vitro inhibition of HHV-1 replication by inosine pranobex and interferon-α Acta Pol Pharm. 2016;73(3):637–644.
13. Tobolska S, Terpilowska S, Jaroszewski J, Siwicki AK. Genotoxicity and mutagenicity of inosine pranobex. J Vet Res. 2018;62(2):207–213.

13. INTERFERON AND INTERFERON INHIBITORS

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Introduction

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

Mechanism of Action

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

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

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

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

Clinical Studies

The IFN response is considered important for the control of coronavirus infection. Interferons have their highest utility in the prophylaxis or early post-exposure management of SARS.[2] In a retrospective cohort study done among pediatric patients with mild to moderate COVID-19, combination interferon alfa aerolization and lopinavir-ritonavir resulted in a complete cure of all 36 patients. Improvement in pneumonia was seen 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 days of treatment and the mean number of days in hospital was 14 days.[6]

In a non-randomized retrospective study, 77 adults hospitalized with confirmed COVID-19 were treated with either nebulized IFN-α2b, arbidol, or a combination of IFN-α2b plus arbidol. Study results showed that treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced duration of elevated blood levels for the inflammatory markers IL-6 and C-reactive protein.[7] Additionally, an open-label non-randomized controlled trial was launched in China to test the efficacy of IFN-α-2b and Lopinavir/Ritonavir versus routine medical treatment in hospitalized patients with SARS-CoV-2 infections.[8] Moreover, there are at least 15 registered clinical trials examining the efficacy of interferons in the treatment of COVID-19 and 1 open label controlled study investigating the efficacy and safety of intravenous administrations of Emapalumab, a monoclonal antibody targeting interferon gamma (Anti-IFNγ), and Anakinra versus standard of care, in reducing hyperinflammation and respiratory distress in patients with SARS-CoV-2 Infection. These studies are either currently recruiting or not yet recruiting. Two studies have completed recruitment but there are no available results yet. Therefore, these findings suggest that IFN should be further investigated as a therapy in COVID-19 cases. (Appendix 11)

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

As of its last update, there have been eight newly registered clinical trials in the US National Library of Medicine ClinicalTrials.gov website investigating the effect of interferon in COVID-19 patients, which are either ongoing recruiting or not yet recruiting.

Results of three other clinical trials were already published. Two trials in Iran evaluated the subcutaneous administration of interferon β-1a in COVID-19. A prospective non-controlled trial evaluated the therapeutic effects of subcutaneous IFN-β-1a administration in remission of symptoms of COVID-19. Twenty patients were

enrolled and received interferon β-1a as adjunct to conventional therapy, including hydroxychloroquine, and lopinavir/ritonavir. Findings support the use of IFN-β-1a in combination with hydroxychloroquine and lopinavir/ritonavir in the management of COVID-19. Fever resolved in all patients after 8 days while some of the symptoms gradually decreased. Results of the virological clearance showed a significant decrease within 10 days and imaging studies showed significant recovery after 14 days in all patients. Furthermore, no deaths or significant adverse reactions were reported within 14 days[11].

Another study was an an open-label randomized clinical trial which studied the efficacy and safety of subcutaneous administration of interferon β-1a as adjunct therapy to standard of care compared to standard of care alone in treatment of severe COVID-19. The study enrolled 42 patients in the treatment group and 39 patients in the control group. Results showed that time to reach the clinical response did not change between groups but there are significantly increased discharge rates on day 14 (OR= 2.5; 95% CI: 1.05- 6.37), significantly reduced mortality if early administration of IFN initiation (OR=13.5; 95% CI: 1.5-118), more extubations (p=0.019), and decreased 28-day mortality in the treatment group compared to the control group (19% vs. 43.6% respectively, p= 0.015)[12].

A single-center, randomized, open-labeled clinical trial was conducted in China which compared the effectiveness of three antiviral treatment regimens involving inhaled interferon among patients with mild to moderate COVID-19. The study enrolled a total of 101 patients with 33 patients in group 1, 36 patients in group 2 and 32 patients in group 3. The three treatment groups were the following: (1) ribavirin (RBV) plus interferon-a (IFN-a), (2) lopinavir/ritonavir (LPV/r) plus IFN-a, and (3) RBV plus LPV/r plus IFN-a at a 1:1:1 ratio. Results showed that that there were no significant differences among the three regimens in terms of antiviral effectiveness. Furthermore, the authors suggested not to administer RBV and LPV/r simultaneously as it is associated with a significant increase in gastrointestinal adverse events.[13]

Recommended Dose

Population	Preparation	Dose
Pedia[9]	Interferon α nebulization	200,000-400,000 IU/kg or 2-4 µg/kg in 2 ml sterile water, nebulization 2x per day for 5-7 days
	Interferon –α2b spray	*Note: Applied for high risk populations with a close contact with suspected 2019-mCoV infected patients OR those in the early phase with only upper respiratory tract symptoms*
	Interferon –α2b spray	1-2 sprays on each side of the nasal cavity, 8-10 spray on the oropharynx
	Interferon –α2b injection	8000 IU, once every 1–2 h, 8–10 sprays/day for 5–7 days
Adult[14]	Interferon α	5 million units or equivalent dose in 2 ml sterile water via vapor inhalation 2x a day for no more than 10 days
	Interferon β-1a[11]	44ug (12million international units) subcutaneously every other day until day 10

	Interferon β-1a[12]	44ug (12million international units) subcutaneously 3x weekly for 2 consecutive weeks

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.[15]

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%). [16]

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

Conclusion

Interferons may have a role in early treatment in coronavirus infections, but more clinical trials are needed to validate this. There is insufficient evidence to conclude its efficacy and safety in the treatment of COVID-19. Use with caution in children.

REFERENCES:

1. Li SF, Gong MJ, Zhao FR, et al. Type I interferons: distinct biological activities and current applications for viral infection. Cell Physiol Biochem 2018; 51:2377-2396. doi: 10.1159/000495897. Epub 2018 Dec 11.
2. Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. Cytokine Growth Factor Rev. 2008; 19(2):121-32. doi: 10.1016/j.cytogfr.2008.01.001. Epub 2008 Mar 5.
3. Prokunina-Olsson L, Alphonse N, Dickenson RE, et al. COVID-19 and emerging viral infections: the case for interferon lambda. J Exp Med. 2020; 217(5). pii: e20200653. doi: 10.1084/jem.20200653.
4. Haagmans BL1, Osterhaus AD. Coronaviruses and their therapy. Antiviral Res. 2006; 71(23):397-403. Epub 2006 Jun 19.
5. Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. J Clin Invest. 2020. pii: 137647. doi: 10.1172/JCI137647. [Epub ahead of print]
6. Qiu H, Wu J, Liang H, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020; published online March 25.
7. Zhou Q, Chen V, Shannon C, et al. Interferon-α2b treatment for COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.04.06.20042580.this version posted April 10, 2020.
8. Xu Z. Clinical efficacy of novel coronavirus infection treated by combination of interferon regimen and Ritonavir tablets. Chinese Clinical Trial Registry ChiCTR2000031196. Available from: http://www.chictr.org.cn/showprojen.aspx?proj=51112. Accessed on: 19 April 2020.
9. Shen KL, Yang Y, Wang T, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020. https ://doi.org/10.1007/s1251 9-020-00343 -7.
10. Jin Y, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Medical Research (2020) 7:4 https://doi.org/10.1186/s40779-020-0233-6.
11. Dastan F, Nadji SA, Saffaei A, Marjani M, Moniri A, Jamaati H, Mohammad S, Hashemian R, Baghaei P, Abedini A, Varahram M, Yousefian S, and Tabarsi P. Subcutaneous administration of interferon beta-1a for COVID-19: A noncontrolled prospective trial. 2020. International Immunopharmacology, 85. Accessed at https://doi.org/10.1016/j.intimp.2020.106688 on 13 August 2020.
12. Davoudi-Monared E, Rahmani H, Khalili H, Haiiabdolbaghi M, Salehi M, Abbasian L, Kazemzadeh H, Yekaninejad MS. Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomized clinical trial. 2020. Antimicrobial Agents and Chemotherapy. *American Society for Microbiology*. Accessed on 13 August 2020. doi:10.1128/AAC.01061-20
13. Huang YQ, Tang SQ, Xu XL, et al. No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study. *Front Pharmacol*. 2020;11:1071. Published 2020 Jul 14. doi:10.3389/fphar.2020.01071
14. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020; 14(1):58–60. doi:10.5582/ddt.2020.01012.
15. Arnaud P. Different interferons: pharmacology, pharmacokinetics, proposed mechanisms, safety and side effects. Rev Med Interne. 2002; 23 Suppl 4:449s-458s.
16. Wang Y, Zhu LQ. Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019. World Journal of Pediatrics https://doi.org/10.1007/s12519-020-00353-5

14. TARGETED MONOCLONAL ANTIBODIES

a. ANTI-GM-CSF or GM-CSF INHIBITORS

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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.

REFERENCES:

1. Palash B, Isadore B, Medha S, et al. Dual Role of GM-CSF as a Pro-Inflammatory and a Regulatory Cytokine: Implications for Immune Therapy.J Interferon Cytokine Res. 2015 Aug 1; 35(8): 585–599. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4529096/. Accessed on: 2020 April 26.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497–506.
3. Mohit S, Philippe D, Stéphane D, et al. Granulocyte-macrophage colony-stimulating factor inactivation in CAR T-Cells prevents monocyte- dependent release of key cytokine release syndrome mediators. J. Biol. Chem 2019; 294(14): 5430–5437. Available from: https://www.jbc.org/content/early/2019/02/25/jbc.AC119.007558.full.pdf. Accessed on: 2020 April 25.
4. Aoi S and Takashi U. Pivotal Roles of GM-CSF in Autoimmunity and Inflammation. Hindawi Publishing Corporation Mediators of Inflammation 2015; Article ID 568543: 13 pages. Available from: http://dx.doi.org/10.1155/2015/568543. Accessed on 2020 April 25.
5. Dhagat U, Hercus T, Broughton S, et al. The mechanism of GM-CSF inhibition by human GM-CSF auto-antibodies suggests novel therapeutic opportunities. MABS 2018; Vol. 10, No. 7: 1018–1029. Available from: https://doi.org/10.1080/19420862.2018.1494107. Accessed on: 2020 April 26.
6. Yonggang Z, Binqing F, Xiaohu Z, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. BioRxiv 2020 Feb 20. Available from: https://www.biorxiv.org/content/10.1101/2020.02.12.945576v1. Accessed on 2020 April 26.
7. Abdurrahman T, Aslıhan AG, Marco M-C. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020; 50: 620-632. Available from: http://journals.tubitak.gov.tr/medical/issues/sag-20-50-si-1/sag-50-si-1-19-2004-168.pdf. Accessed on 2020 April 26.
8. https://www.creativebiolabs.net/lenzilumab-overview.htm. Accessed on 2020 April 27.
9. https://www.morphosys.com/pipeline/proprietary-product-portfolio/mor103. Accessed on 2020 July 27.
10. Mavrilimumab, a Fully Human Granulocyte–Macrophage Colony-Stimulating Factor Receptor α Monoclonal Antibody. Long-Term Safety and Efficacy in Patients With Rheumatoid Arthritis Burmester G, McInnes I, Kremer J, et al. Arthritis Rheumatol 2018 May; 70(5): 679–689. Accessed on 2020 July 27.
11. https://clinicaltrials.gov/ct2/results?cond=Covid19&term=Anti+GM-CSF&cntry=&state=&city=&dist=. Accessed on 2020 July 27.

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

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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, case reports of patients with COVID-19 treated successfully with anakinra have been published. One was on a patient who refused ventilatory support,[12] the next was a patient with hepatic involvement,[13] another with complicated pericarditis,[14] another one with steroid intolerance,[15] and the last one was a patient who was refractory to antivirals and anti-IL-6.[16]

Several case series have also been published. First, a prospective case series of 9 consecutive moderate to severe COVID-19 pneumonia patients at high risk of worsening were given anakinra for 10 days. Results showed good clinical and biologic outcomes for 8 of the 9 patients.[17] Next was a case series of 5 patients who had resolution of systemic inflammation and improvement in respiratory parameters.[18] Anakinra was likewise shown to be safe in 3 patients with acute leukemia and COVID-19.[19] A retrospective case series showed that early initiation of anakinra prevented mechanical ventilation because all 7 of those who were given anakinra less than 36 hours after onset of acute hypoxic respiratory failure did not require mechanical ventilation; 4 patients who were given anakinra after 4 days required mechanical ventilation, 3 were eventually extubated but 1 died. Three patients met their inclusion criteria but were not given anakinra; all 3 also required mechanical ventilation.[20] Another case series of 8 patients with COVID-19 who had secondary hemophagocytic lymphohistiocytosis reported improvement in respiratory function at the end of treatment (7 days) although 3 later died of refractory shock; the authors reported that the mortality was still lower than historical series of patients with sHLH in sepsis.[21] (Appendix 12-A)

A retrospective cohort of severe COVID-19 patients given anakinra was compared to historical control. Result showed that the need for invasive mechanical ventilation or death occurred in 13 (25%) of 52 patients in the anakinra group compared with 32 (73%) of 44 patients in the historical group (HR 0.22 [95% CI 0.11–0.41; p<0.0001).[22] Another retrospective cohort study included 29 patients in the high dose anakinra group, 7 patients in the low dose anakinra group and 16 patients in the standard treatment group. At 21 days, survival was 90% in the high-dose anakinra group and 56% in the standard treatment group (p=0.009). Treatment with low dose anakinra was stopped after 7 days because of paucity of effects in CRP and clinical status.[23] The most recent study is a small cohort of 12 COVID-19 pneumonia patients who received anakinra early (between the 5th and 13th day of diagnosis); their matched control group were patients who received standard of care. Clinical improvement was observed in the patients who received anakinra.[24] Lastly, there is one retrospective cohort which compared anakinra to tocilizumab. Results showed that the risk of death was lower in the anakinra group (22.0%) than the tocilizumab group (46.2%); the percentage of anakinra treatment responders was correspondingly higher (63.4% vs 43.2%). However, the authors saw that there was a survival advantage with anakinra compared to tocilizumab treated patients. After adjustment for multiple baseline imbalances this difference did not reach statistical significance (PS-adjusted HR=0.46, 95%CI= 0.18-1.20, p=0.11).[25]

Based on these observational and small cohort studies, reliable conclusions cannot yet be drawn with regards anakinra's efficacy and safety; stronger evidence with clinical trials are needed. There are currently 15 clinical trials registered in ClinicalTrials.gov using anakinra, alone or in combination with other immunomodulators, for COVID-19[26] and 4 studies using canakinumab.[27]

Recommended Dose

In various ongoing clinical trials (in ClinicalTrials.gov[26,27]), 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)[28]
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]

Conclusion

Published studies for IL-1 receptor antagonists are limited to anakinra. The use of anakinra to prolong survival in cytokine storm syndrome (CSS) are either observational studies or small cohort studies; hence, its use for COVID-19 CSS should still be in the context of a clinical research, pending results of large clinical trials.

REFERENCES:

1. Cavalli G and Dinarello CA. Anakinra therapy for non-cancer inflammatory diseases. Front Pharmacol. 2018; 9:1157. doi: 10.3389/fphar.2018.01157.
2. Sahoo M, Ceballos-Olvera I, Del barrio L , Re F. Role of the inflammasome, IL-1β and IL-18 in bacterial infections. ScientificWorldJournal. 2011; 11:2037-2050. doi: 10.1100/2011/212680.
3. Shrivastava G, Leon-Jaurez M, Garcia-Cordero J, et al. Inflammasomes and its importance in viral infections. Immunol Res. 2016; 64:1101-1117. doi: 10.1007/s12026-016-8873-z.
4. Cohen SB, Rubbert A. Bringing the clinical experience with anakinra to the patient. Rheumatology. 2003; 42(Suppl. 2):ii36–ii40. doi:10.1093/rheumatology/keg331.
5. Highlights of prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125249lbl.pdf. Accessed 5 April 2020.
6. Canakinumab - drug summary. Available from: https://www.pdr.net/drug-summary/Ilaris-canakinumab-434.8451. Accessed 5 April 2020.
7. Russell B, Moss C, Gincy G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19 – a systematic review of current evidence. E-cancermedicalscience. 2020; 14:1022. doi: 10.3332/ecancer.2020.1022.
8. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med. 1997; 25(7):1115–24.
9. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. Crit Care Med. 2016; 44:275–81.
10. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. ACR Open Rheumatol. 2020 Apr 8. doi: 10.1002/acr2.11135. [Epub ahead of print].
11. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. Arthritis Rheumatol. 2020; 72(2):326-334. doi: 10.1002/art.41103.
12. Figeuro-Perez L, Olivares-Hernandez A, Escala-Cornejo RA, et al. Anakinra, una alternativa potencial en el tratamiento de la infección respiratoria grave por SARS-CoV-2 refractaria a tocilizumab. Rheumatol Clin. 2020; doi: 10.1016/j.reuma.2020.06.003 [Epub ahead of print].
13. Gonzalez-Garcia A, Garcia-Sanchez I, Lopes V, et al. Successful treatment of severe COVID-19 with subcutaneous anakinra as a sole treatment. Rheumatology. 2020; 59(8):2171-2173. doi: 10.1093/rheumatology/keaa318.
14. Karadeniz H, Yamak BA, Ozger HS, et al. Anakinra for the treatment of COVID-19-associated pericarditis: a case report. Cardiovasc Drugs Ther. 2020; doi: 10.1007/s10557-020-07044-3 [Epub ahead of print].
15. Filocamo G, Mangior D, Aliberti S, et al. Use of anakinra in severe COVID-19: a case report. Int J Infect Dis. 2020; 96:607-609. doi: 10.1016/j.ijid.2020.05.026.

16. Franzetti M, Pozzetti U, Carugati M, et al. Interleukin-1 receptor antagonist anakinra in association with remdesivir in severe COVID-19: a case report. Int J Infect Dis. 2020; 97: 215–218. doi: 10.1016/j.ijid.2020.05.050.
17. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020. pii: annrheumdis-2020-217706. doi: 10.1136/annrheumdis-2020-217706. [Epub ahead of print].
18. Pontali E, Volpi S, Antonucci G, et al. Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease. J Allergy Clin Immunol. 2020 Jul; 146(1): 213–215. doi: 10.1016%2Fj.jaci.2020.05.002.
19. James JW, Fox TA, Halsey R, et al. Interleukin-1 blockade with anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement. r J Haematol. 2020; 190(2):e80-e83. doi: 10.1111/bjh.16873.
20. Navarro-Millan I, Sattui SE, Lakhanpal A, et al. Use of anakinra to prevent mechanical ventilation in severe COVID-19: a case series. Arthritis Rheumatol. 2020; doi: 10.1002/art.41422 [Epub ahead of print].
21. Dimopoulos G, de Mast Q, Markou N, et al. Favorable anakinra responses in severe COVID-19 patients with secondary hemophagocytic lymphohistiocytosis. Cell Host Microbe. 2020 Jul 8; 28(1): 117–123.e1. doi: 10.1016/j.chom.2020.05.007.
22. Cavalli G, De Luca G, Campochiari C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020; 2(6):e325-e331. doi: 10.1016/S2665-9913(20)30127-2.
23. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020; 2(7):e393-e400. doi: 10.1016/S2665-9913(20)30164-8.
24. Cauchois R, Koubi M, Delarbre D, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A. 2020; 202009017. doi: 10.1073/pnas.2009017117.
25. Langer-Gould A, Smith JB, Gonzales EG, et al. Early identification of COVID-19 cytokine storm and treatment with anakinra or tocilizumab. Int J Infect Dis. 2020; S1201-9712(20)30609-3. doi: 10.1016/j.ijid.2020.07.081. [Epub ahead of print].
26. U.S. National Library of Medicine. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=anakinra&cntry=&state=&city=&dist=. Accessed 13 August 2020.
27. U.S. National Library of Medicine. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=canakinumab&cntry=&state=&city=&dist=. Accessed 13 August 2020.
28. Halyabar O, Chang MH, Schoettler ML, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Pediatr Rheumatol Online J. 2019; 17:7. doi: 10.1186/s12969-019-0309-6.

c. ANTI-INTERLEUKIN 6 (IL–6) or IL–6 INHIBITORS

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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

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

There are 14 observational studies , 1 case report and 64 registered clinical trials on the use of tocilizumab for COVID-19 patients. (Appendix 12-B). Two clinical trials were completed and pending publication of results.

A multi-site, randomized, double-blind, placebo-controlled phase III study evaluated the safety and efficacy of intravenous tocilizumab added to standard of care in adult patients hospitalized with severe COVID-19 associated pneumonia compared to placebo plus standard of care (NCT04320615). Initial results of this study showed no improvement in the clinical status of those who received tocilizumab compared to those who received the placebo (OR 1.19; 95% CI 0.81- 1.76). Time to hospital discharge was shorter in patients treated with tocilizumab (median 20 days; 95% CI 17-27) than in those treated with placebo (median 28.0; 95% CI 20.0, NE) (p=0.0370). No new safety signals were identified in the study.[7]

In a phase 2, non-randomized, open-label trial, 32 adult patients with COVID-19 were given low-dose tocilizumab (NCT04331795).[8] The patients included in the trial were those with radiographic pulmonary infiltrates, fever, CRP of ≥ 40 mg/L, and did not require mechanical ventilation. Rapid resolution of fever and CRP decline were observed in majority of those who received tocilizumab (40-200 mg) compared to the retrospective controls.

Tocilizumab was given to 21 patients with severe or critical COVID-19 pneumonia. The body temperature of all patients returned to normal after one day of tocilizumab. Majority of the patients had improvements in their peripheral oxygen saturation, CRP levels and chest CT scans.[9]

In a prospective open, single-arm multicenter study of 63 patients with severe COVID-19, the use of tocilizumab within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2; 95%CI 1.3–6.7).[10]

A single-center case-control study on the use of siltuximab in adult COVID-19 patients with ARDS is ongoing (NCT04322188). Interim data showed reduced need for ventilation for most of the included patients.[11]

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

The Chinese Clinical Guidance for COVID-19[12]and the Italian Society of Infectious Diseases and Tropical Diseases COVID-19 Guideline[13] have recommended the use of tocilizumab as a treatment option for patients with severe COVID-19.

Recommended Dose

A. Tocilizumab:
   Adult dose:
   - 8 mg/kg (maximum: 800 mg/dose) as a single dose; may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve[14]
   - 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[15]

   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[16]

B. Sarilumab: 400 mg single IV dose or 200-400 mg SC dose[17]
C. Siltuximab: 11 mg/kg infused over one hour with a potential second dose at the physician's discretion[11]

Adverse Effects

In the observational study for COVID-19 patients, there have been no reports of subsequent pulmonary infection, deterioration of illness nor death among those given tocilizumab. There were likewise no adverse drug reactions reported.[9]

Tocilizumab was associated with an increased risk of infectious respiratory adverse events in patients with rheumatoid arthritis.[18] Both tocilizumab and sarilumab carry FDA black box warnings of serious infections, such as tuberculosis and invasive fungal infections, leading to hospitalization or death.

Conclusion

Initial results of the completed phase 3 clinical trial on tocilizumab showed no clear clinical benefit for severe COVID-19 pneumonia. There is limited evidence to evaluate the efficacy and safety of siltuximab on patients with COVID-19. There are no completed clinical trials for Sarilumab at present. More data from ongoing and planned clinical trials are needed to establish the role of IL-6 inhibitors in the management of such patients.

REFERENCES:

1. Shimabukuro-Vornhagen A, Godel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018; 6:56. https://dx.doi.org/10.1186%2Fs40425-018-0343-9
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497-506.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054-1062.
4. Wang Z, Yang B, Li Q, et al. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clinical Infectious Diseases. 2020; 71:769-777.
5. Zhang C, Wu Z, Li JW, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce in the mortality [published online ahead of print, 2020 Mar 28]. Int J Antimicrob Agents. 2020; 55:105954.
6. Le R, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncol. 23 (2018); 943–947.
7. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed on August 03, 2020.
8. Strohbehn GW, Heiss BL, Rouhani SJ, et al. COVIDOSE: Low-dose tocilizumab in the treatment of Covid-19. MedRxiv. 2020. doi: 10.1101/2020.07.20.20157503.
9. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020; 117:10970-10975.
10. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol 2020; 38:529-532.
11. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. MedRxiv 2020. doi: 10.1101/2020.04.01.20048561.
12. American College of Cardiology. Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment. Available from: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/11/22/chinese-clinical-guidance-for-covid-19-pneumonia-diagnosis-and-treatment. Accessed on August 31, 2020.
13. Italian Society of Infectious and Tropical Diseases. Guideline for the treatment of people with COVID-19 disease. 2020. Available from: https://www.acep.org/globalassets/images/italian-guidelines-for-covid-19-google-translate.pdf.pdf. Accessed on August 31, 2020.
14. Genentech Inc. Actemra use in coronavirus disease 2019 (COVID-19) [press release]. South San Francisco, CA: Genentech, a member of the Roche Group. Available from: https://www.google.com/search?client=safari&rls=en&q=Actemra+use+in+coronavirus+disease+2019+(COVID-19)&ie=UTF-8&oe=UTF-8. Accessed on August 31, 2020.
15. Philippine Society for Microbiology and Infectious Diseases. Interim Guidelines in the Management Adult Patients with Suspected or Confirmed COVID-19 Infections.Version 2.1 as of 31 March 2020. Available from: https://www.psmid.org/interim-management-guidelines-for-covid-19-version-3-1/. Accessed on April 14, 2020.
16. National Institutes of Health (NIH). Tocilizumab in COVID-19 pneumonia. Updated March 20, 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT043170921. Accessed on April 14, 2020.
17. National Institutes of Health (NIH). Tocilizumab in COVID-19 pneumonia. Updated April 6, 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04315298. Accessed on April 14, 2020.

18. Geng Z, Yu Y, Hu S, et al. Tocilizumab and the risk of respiratory adverse events in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomised controlled trials. Clinical and experimental rheumatology. 2019;37(2):318-23.

d. ANTI-TNF or TNF INHIBITORS

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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 is an ongoing prospective, single center, phase II trial evaluating the efficacy of infliximab or infliximab-abda in hospitalized adult patients with severe or critical COVID-19.[3]

There is one registered clinical trial on the efficacy and safety of adalimumab for severe COVID-19 pneumonia.

Recommended Dose

In an ongoing trial on infliximab for treatment of severe or critical COVID-19 patients, the dose being given is 5mg/kg/day IV. A second dose of infliximab may be given 7-21 days following the primary therapy.[3]

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.[4] In children common adverse reactions include infections such as upper respiratory tract infection, nasopharyngitis

and headache. Pneumonia was identified as the most common serious adverse reaction.[5]

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

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

Conclusion

There are no completed studies on the use of TNF inhibitors for the treatment of COVID-19. A clinical trial is currently being conducted in the United States.

REFERENCES:

1. Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! [published online ahead of print, 2020 Mar 20]. Autoimmun Rev. 2020;102523. doi:10.1016/j.autrev.2020.102523
2. Steihm's Immune Deficiencies 2014 https://www.sciencedirect.com/science/article/pii/B9780124055469000492
3. National Institutes of Health (NIH). A Phase 2 Trial of Infliximab in Coronavirus Disease 2019 (COVID-19). Updated June 11, 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04425538. Accessed on 7 August 2020,
4. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013;72(4):517–524. doi:10.1136/annrheumdis-2011-201244
5. Horneff G, Seyger MMB, Arikan D, et al. Safety of Adalimumab in Pediatric Patients withPolyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease. J Pediatr. 2018;201:166–175.e3. doi:10.1016/j.jpeds.2018.05.042
6. Website: https://www.mims.com/philippines/drug/info/humira/drug-interactions

e. 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

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

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

Recommendad Dose:

700 mg subcutaneous[2]

Adverse Effects

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

Conclusion

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

REFERENCES:

1. https://aidsinfo.nih.gov/drugs/423/leronlimab/0/patient
2. Patterson B, Seethamraju H, Dhody K, et al Disruption of the CCL5/RANTES-CCR5 Pathway Restores Immune Homeostasis and Reduces Plasma Viral Load in Critical COVID-19 Medrxiv.org May 5, 2020. Available from https://www.medrxiv.org/content/10.1101/2020.05.02.20084673v1. Accessed on April 28, 2020

f. INTERLEUKIN 2

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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.

REFERENCES:

1. Malek, T. R. The biology of interleukin-2. Annu. Rev. Immunol. 26, 453–79 (2008)
2. Boyman, O. & Sprent, J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat. Rev. Immunol. 12, 180–90 (2012).
3. Liao, W., Lin, J. X. & Leonard, W. J. Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. Immunity 38, 13–25 (2013).
4. Zheng, S. G. et al. IL-2 is essential for TGF-beta to convert naive CD4+CD25- cells to CD25+Foxp3+ regulatory T cells and for expansion of these cells. J. Immunol. 178, 2018–27 (2007).
5. Ye, C., Brand, D., & Zheng, S. G. (2018). Targeting IL-2: an unexpected effect in treating immunological diseases. Signal Transduction and Targeted Therapy, 3(1). doi: 10.1038/s41392-017-0002-5
6. Rosenzwajg, M., Lorenzon, R., Cacoub, P., Pham, H. P., Pitoiset, F., Soufi, K. E., Klatzmann, D. (2018). Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. Annals of the Rheumatic Diseases, 78(2), 209–217. doi: 10.1136/annrheumdis-2018-214229
7. Prometheus Laboratories Inc. Proleukin: full prescribing information, May 23, 2019. DailyMed. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4e2b687e-47f2-4f3c-80ab-e3224befffca. Accessed September 23, 2019
8. Paredes R, López Benaldo de Quirós J, Fernández-Cruz E, Clotet B, Lane H. The potential role of interleukin-2 in patients with HIV infection. *AIDS Rev*. 2002; 4(1) : 36-40.
9. Klatzmann D., Abbas A.K. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. Nat Rev Immunol 2015; 15:283-294.

10. Yu A, Snowhite I, Vendrame F, Rosenzwajg M, Klatzmann D. Pugliese A, et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms supports the use of low-dose IL-2 therapy in type 1 diabetes. Diabetes. 2015; 64: 2172-2183.
11. Saadoun D, Rosenzwaijg M, Joly F, Six A, Carrat F, Thibault V, et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl Med. 2011; 365: 2067-2077
12. How proleukin works.https://www.proleukin.com/hcp.Accessed 2 May 2020
13. Bonnet B., Vigneron J., Levacher B., Vazquez T., Pitoiset F., Brimaud F., et al.; Low-dose IL-2 induces regulatory T cell-mediated control of experimental food allergy. J Immunol. 2016; 197: 188-198
14. Konrad M.W., Hemstreet G., Hersh E.M., Mansell P.W., Mertelsmann ., Kolitz J.E., et al.; Pharmacokinetics of recombinant interleukin 2 in humans. Cancer Res. 1990; 50: 2009-2017
15. Churlaud, G., Abbara, C., Vinot, P-A., Fourcade, G., Ritvo, P.-G., Lorenzon, R., Klatzmann, D. (2018). Pharmacodynamics of regulatory T cells in mice and humans treated with low-dose IL-2. Journal of Allergy and Clinical Immunology, 142(4). doi: 10.1016/j.jaci.2018.06.006
16. Interleukin-2 Drug Information, Chemocare. Copyright 2002-2020.

g. JAK 1 & 2 INHIBITORS

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Introduction

JAK 1 and 2 inhibitors currently being studied for the treatment of COVID-19 include baricitinib, ruxolitinib and jacketinib. The use of fedratinib in the treatment of COVID-19 is being proposed. 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] Jacketinib is still in its phase II clinical trials for the treatment of myelofibrosis, severe alopecia areata, idiopathic pulmonary fibrosis, rheumatoid arthritis, ankylosing spondylitis, severe plaque psoriasis; and moderate to severe atopic dermatitis.[7] Fedratinib is a newly licensed treatment for myeloproliferative neoplasm-associated myelofibrosis in 2020.[8]

Mechanism of Action

Baricitinib, jacketinib, fedratinib 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 blocks the production of these cytokines thereby dampens the inflammatory response by the host.[4,7,8, 9, 10]

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.[9,10]

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.[11]

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 with baracitinib is high because of its low plasma protein binding and minimal interaction with CYP enzymes and drug transporters. There is the potential for combining baricitinib with the direct acting antivirals (lopinavir or ritonavir and remdesivir) currently being used in the COVID-19 outbreak, since it has a minimal interaction with the relevant CYP drug metabolizing enzymes.[12]

Clinical Studies

A non-peer reviewed article on in vitro testing of anti-SARS-CoV-2 activities of several drugs reported that baricitinib showed no inhibitory activities against SARS - CoV-2 at the concentration of 3 μM or 3.2 μM.[13] Three (3) case report studies done in Italy showed successful recoveries in COVID-19 patients who were given baricitinib. Two studies from the ClinicalTrials.gov on baricitinib for COVID-19 have completed the trials. The first study, a non-randomized, open-label, cross-over trial, showed significant improvement clinically of laboratory parameters in the baricitinib group. None of them required ICU support and majority (7/12) were discharged at week 1 and 2 after the start of treatment (p=0.027).[14] In the second study, a retrospective cohort, 12 (73.3%) patients given baricitinib recovered with normal body temperature and decreased inflammatory markers and need for oxygen support. However, 3 (13.3%) patients who were not given baricitinib died due to secondary bacterial or fungal infections during prolonged ICU stays.[15](Appendix 11) Wu D. et al concluded in their reviews that fedratinib can suppress the production of several TH17 signature cytokines, therefore promising to prevent the deteriorating outcomes of TH17 associated cytokine storm in COVID-19.[16]

Fourteen clinical trials of baricitinib, 20 of ruxolitinib and 1 of jacketinib in COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future. (Appendix 12-C)

Recommended Dose

Baricitinib:[17]

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

Pediatric dose: Safety and efficacy not established

Ruxolitinib:[18]

Adult dose: 10mg twice daily for 14 days

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

Jacketinib:[19]

Adult dose: 50-100mg twice daily for 7 consecutive days

Pediatric dose: Safety and efficacy not established

Fedratinib:[20]

Adult dose: 200-400 mg orally once a day

Pediatric dose: 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.[17] Ruxolitinib and fedratinib, on the other hand are associated with peripheral blood cytopenia,

hyperlipidemia and elevated liver enzymes.[17, 20] Ruxolitinib may also cause viral as well as bacterial infections.[18] Wernicke's encephalopathy has occurred in patients treated with fedratinib. Fedratinib should not be started in patients with thiamine deficiency.[20]

Conclusion

There are only 2 clinical trials that concluded the effectiveness and safety of baricitinib in the treatment of COVID 19. Findings of the ongoing studies of JACK 1 and 2 inhibitors will help strengthen their use in this setting.

REFERENCES:

1. Bechman K, Subesinghe S, Norton S, et al. A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatology (Oxford). 2019 Oct 1;58(10):1755-1766. doi: 10.1093/rheumatology/kez087.
2. Kunwar S, Collins CE, Constantinescu F. Baricitinib, a Janus kinase inhibitor, in the treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. Clinical Rheumatology. 2018 Oct;37(10):2611-2620. doi: 10.1007/s10067-018-4199-7.
3. Harigai M, Takeuchi T, Smolen JS, et al. Safety profile of baricitinib in Japanese patients with active rheumatoid arthritis with over 1.6 years median time in treatment: An integrated analysis of Phases 2 and 3 trials. Modern Rheumatology. 2020 January; 30(1), 36-43. https://doi.org/10.1080/14397595.2019.1583711.
4. Mascarenhas J, Hoffman R. Ruxolitinib: The First FDA Approved Therapy for the Treatment of Myelofibrosis. Clin Cancer Res. 2012 June; 18(11):3008-3014. https://clincancerres.aacrjournals.org/content/early/2012/05/09/1078-0432.CCR-11-3145.
5. Raedler LA. Jakafi (Ruxolitinib): First FDA-Approved Medication for the Treatment of Patients with Polycythemia Vera. American Health & Drug Benefits. 2015 March; 8:75-79. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4665047/pdf/ahdb-08-075.
6. Przepiorka D, Luo L, Subramaniam S, et al. FDA Approval Summary: Ruxolitinib for Treatment of Steroid Refractory Acute Graft-Versus-Host Disease. The Oncologist. 2019 October; 25: e328–e334. https://theoncologist.onlinelibrary.wiley.com/doi/epdf/10.1634/theoncologist.2019-0627.
7. Suzhou Zelgen Biopharmaceuticals Co., Ltd. Zelgen Pharmaceutical Jacketinib Hydrochloride Tablets Approved for Phase II Clinical Trial in the Treatment of Moderate and Severe Atopic Dermatitis. CMO CRO Pharma Circle Company Press Release. 2020 March. https://www.cmocro.com/news_detail/Zelgen+Pharmaceutical+Jacketinib+Hydrochloride+Tablets+Appro/471392/index.html;
8. Talpaz M, Kiladjian JJ. Fedratinib, a newly approved treatment for patients with myeloproliferative neoplasm-associated myelofibrosis. Leukemia. 2020 July. doi:10.1038/s41375-020-0954-2.
9. Favalli EG, Ingegnoli F, De Lucia O, et al. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity Reviews. 2020 May; 19 (5): 102523. https://doi.org/10.1016/j.autrev.2020.102523.
10. Zhang W, Zhao Y, Zhang F, et al., The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clinical Immunology. 2020 May; 214 108393. doi:10.1016/j.clim.2020.108393.
11. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020 February; 395: e30-e31. doi: 10.1016/SO140-6736(20)30304-4.
12. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020 April; 20: 400-402. Doi:10.1016/S1473-3099(20)30132-8.
13. Ge Y, Tian T, Huang S, et al. A data driven drug repositioning framework discovered potential therapeutic agent targeting COVID-19. BioRxiv. March 2020. doi:10.1101/2020.03.22986836.

14. Cantini F, Niccoli L, Matarrese D, et al. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. 2020;81(2):318–356.
15. Titanji BK, Farley MM, Mehta A, et al. Use of Baricitinib in patients with moderate and severe COVID-19. Clin. Infect. Dis. 2020 doi: 10.1093/cid/ciaa879.
16. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect*. 2020;53(3):368-370. doi:10.1016/j.jmii.2020.03.005
17. Baricitinib (Rx) Drugs and Diseases, Medscape.
18. Ruxolitinib (Rx) Drugs and Diseases, Medscape.
19. Lu H, et al. Study for safety and efficacy of Jakotinib hydrochloride tablets in the treatment severe and acute exacerbation patients of novel coronavirus pneumonia (COVID-19). Chinese clinical trial registry. http://www.chictr.org.cn/showprojen.aspx?proj=50017.
20. Fedratinib (Rx) Drugs and Diseases, Medscape.

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]

MSC have also been shown to improve the lung microenvironment, pulmonary fibrosis, and lung function, probably due to the regulation of the inflammatory response and the promotion of tissue repair and regeneration.[5]

Clinical Studies

The pilot trial published using intravenous umbilical cord (UC)-derived MSC was done in 7 patients with COVID-19 infected pneumonia who received one dose of stem cell therapy, compared to 3 patients in the control group (3 serious). Results showed improved pulmonary function, but no clear general trend in terms of inflammatory cytokines and T-regulatory cells. Limitations of this study include the small sample size and short-term follow-up.[5]

Since then, there have been 3 other published reports. Umbillical cord derived mesenchymal stem cells (UC-MSC) was used for the treatment of 31 patients with severe COVID-19 pneumonia at Taikangtongji Hospital in Wuhan, China. This demonstrated that the treatment could restore oxygenation and downregulate cytokine without any infusion reaction.[6]

A non-randomized open-label cohort study addressed the safety and efficacy of exosomes (ExoFlo™) derived from allogeneic bone marrow mesenchymal stem cells as treatment for 24 patients with severe COVID-19 and moderate-to-severe acute respiratory distress syndrome at a single hospital center. They reported a survival rate of 83%. And overall, there was improvement of clinical status, immune reconstitution and downregulation of cytokine storm.[7]

A clinical pilot study used menstrual blood-derived MSCs for the treatment of 2 patients with severe COVID-19 in Wuhan. It reported improvement in oxygenation, increase in immune indicators and decrease in inflammatory indicators after treatment.[8]

There are 55 other studies listed in ClinicalTrials.gov using MSC for COVID-19 that are either in the process of gathering data, recruiting subjects or have not yet started.[9]

Adverse Reactions

Safety and effectiveness of MSCs have been documented in several clinical trials.[10,11] However, numerous complications have been reported from improper application of stem cells.[12] 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.[13]

Also, during IV infusion, all precautions should be taken to prevent pulmonary or other organ embolization. Patients should be monitored for allergic reactions especially when using allogeneic products.[13]

Conclusion

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

REFERENCES:

1. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy, 2006; 8(4): 315–317.
2. Wilson JG, Liu KD, Zhuo NJ, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med 2015; 3:24-32.
3. Hashmi S, Ahmed M, Murad MH, et al. 2016. Survival after mesenchymal stromal cell therapy in steroid refractory acute graft-versus-host disease: systematic review and meta-analysis. Lancet Haematol 2016; 3(1):E45-E52.
4. Abraham A, Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. Stem Cells Transl Med 2020; 9:28-38.
5. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2 mesenchymal stem cells improves the outcomes of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216-228.
6. Guo Z, Chen Y, Luo X, et al. Administration of umbilical cord mesenchymal stem cells in patients with severe COVID-19 pneumonia. Crit Care 2020; 24: 420.
7. Sengupta V, Sengupta S, Lazo A, et al. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19. Stem Cells Dev 2020; 29(12):747-754.
8. Tang L, Jiang Y, Zhu M, et al. Clinical study using mesenchymal stem cells for the treatment of patients with severe COVID-19. Front Med 2020: 1-10. doi: 10.1007/s11684-020-0810-9.
9. ClinicalTrials.gov.Availablefrom:https://clinicaltrials.gov/ct2/results?cond=covid+19&term=mesenchymal++stem+cells&cntry=&state=&city=&dist=
10. https://clinicaltrials.gov/ct2/results?cond=COVID&term=mesenchymal+stem+cells&cntry=&state=&city=&dist=. Accessed on August 13, 2020.
11. Kamen DL, Nietert PJ, Wang H, et al. 2018. CT-04 Safety and efficacy of allogeneic umbilical cord-derived mesenchymal stem cells (MSCs) in patients with systemic lupus erythematosus: results of an open-label phase I study. Lupus Sci Med 2018; 5:A46-A47
12. Golchin A, Farahany T Z, Khojasteh A, et al. The clinical trials of mesenchymal stem cell therapy in skin diseases: An update and concise review. Curr Stem Cell Res Ther 2019; 14(1): 22–33. doi: https://doi.org/10.2174/1574888x13666180913123424.
13. Bauer G, Elsallab M, Abou-El-Enein M. Concise review: a comprehensive analysis of reported adverse events in patients receiving unproven stem cell based interventions. Stem Cells Transl Med 2018; 7(9):676-685.
14. Atluri S, Manchikanti L, Hirsch JA. Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: the case for compassionate use. Pain Physician. 2020; 23(2):E71-E83.

16. RELEASE ACTIVE ANTIBODIES TO HUMAN INTERFERON GAMMA

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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.

REFERENCES:

1. Tarasov SA, Kachanova MV, Gorbunov EA, et al. Anaferon, released-active form of antibodies to IFN-γ, as an effective medicine for treatment and prophylaxis of a wide spectrum of infections. Clin Res Trials 2016; Vol 2: 229-232. Available from: https://www.oatext.com/pdf/CRT-2-152.pdf
2. Obraztsova EV, Osidak LV, Golovacheva EG, et al. Interferon Status in Children during Acute Respiratory Infections, Therapy with Interferon. Bulletin of Experimental Biology and Medicine 2009; Vol.148, Suppl 1: 275-8. Available from: https://link.springer.com/content/pdf/10.1007/s10517-009-0702-0.pdf
3. Erman ES, Osidak LV, Sukhovetskaya VF, et al. Efficiency of Interferon Inductor Anaferon (Pediatric Formulation) in prophylaxis of acute respiratory infections in sickly Children. Bulletin of Experimental Biology and Medicine 2009; Vol.148, Suppl 1: 18-21.
4. Kokoreva SP, Trushkina AV, Razuvaev OA. Optimization of etiotropic therapy of acute respiratory viral infections in children. Pediatric Infections 2013; No.4: 42- 46.
5. Tarasov S, Zarubaev V, Gorbunov E, et al. Activity of ultra-low doses of antibodies to gamma-interferon against lethal influenza A (H1N1) 2009 virus infection in mice. Antiviral Research 2012; Vol 93: 219-224.
6. Timchenko VN, Pavlova EB, Chernova TM, et al. Evaluation of the Efficiency and Safety of Anaferon (Pediatric Formulation) in the Treatment of Chickenpox in Children. Bulletin of Experimental Biology and Medicine 2009; Vol.148, Suppl 1: 39-42.
7. Epstein O.I., Shtark M.B., Dygai A.M., Sergeyeva S.A., Goldberg E.D., Petrov V.I., Voronina T.A., Starostina M.V. , Pharmacology of ultralow doses of antibodies to endogenous function regulators (M. Publishing House of RAMS,2005) p226

17. STATINS

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.

REFERENCES:

1. Zhaohai Z, Fang P, Buyun X, et al.et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. Journal of Infection 2020; 15: 12. Available from: https://doi.org/10.1016/j.jinf.2020.04.021
2. Cevik M, Bamford C, Ho A, et al. COVID-19 pandemic – A focused review for clinicians. Clinical Microbiology and Infection 2020. Available from: https://doi.org/10.1016/j.cmi.2020.04.023
3. Rationale for Consideration of Statins for COVID-19 Patients. Available from: https://www.massgeneral.org
4. Castiglione V, Chiriacò M, Emdin M, et al. Statin therapy in COVID-19 infection. European Heart Journal-Cardiovascular pharmacotherapy 2020 April 29; pvaa042. Available from: https://doi.org/10.1093/ehjcvp/pvaa04
5. ESC Guidance for the Diagnosis and Management of CV Disease during COVID 19 Pandemic. The European Society of Cardiology, April 21, 2020

18. SUPPLEMENTS

a. VITAMIN C AND QUERCETIN

Beatrice S. Vicente Pascual, MD, Caroline T. Gloria, MD, Cesar Joseph C. Gloria, MD

Introduction

There is current evidence that Vit C and quercetin co-administration exerts a synergistic antiviral action. This is attributed to the overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy.

Mechanism of Action

Quercetin-3B-galactoside binds SARS-CoV-3CL protease (3CLpro) and inhibits its proteolytic activity. This inhibitory action on 3CLpro is dependent on the hydroxyl group of quercetin which recognizes Gln189 as a crucial site on 3CLpro responsible for binding of quercetin[2].

Quercetin exerts a synergistic antiviral action with Vit C. Quercetin spontaneously oxidizes to form O-semiquinone and O-quinone/quinone methide (QQ), which can bind protein thiols forming toxic compounds[3]. This process of both anti- and pro-oxidant effects has been named the "*quercetin paradox*"[4]. However, QQ can be recycled into quercetin by electron donors like NADH or ascorbate, or form together, with glutathione either 6-glutathionyl-quercetin or 8-glutathionyl-quercetin (GSQs)[5,6]. Importantly, if ascorbate or glutathione levels are *insufficient*, quercetin may be shunted to QQ and exert prooxidant effects. Therefore, we stress the importance for its co-administration with vitamin C[7,8].

Clinical Studies

No clinical studies are available at this time.

Recommended Dose

	Quercetin	Vitamin C
Prophylaxis	250 – 500 mg BID	500 mg BID
Mild cases	250 – 500 mg BID	500 mg BID
Severe cases*	500 mg BID	3 gr q6 for 7 days

*ARDS-like presentation, require assisted ventilation/intubation, ICU hospitalization.[1]

Adverse Effect

Oral supplementation with quercetin up to 1 g/day for 3 months has not resulted in significant adverse effects[9]. 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)(10). 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)[11]. Only higher intravenously administered doses up to 51.3 mg/Kg (around 3,591 mg per individual) were associated with renal toxicity[9]. The safety of quercetin-based oral supplementation during pregnancy and breastfeeding has not been established.

Conclusion

Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of the global health pandemic. The use of Vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacologic agents such as Remdesivir and convalescent plasma seem promising. Clinical trials in humans are needed to establish its efficacy and safety.

REFERENCES:

1. Colunga Biancatelli RML, Berrill M , Catravas John D, Mark PE. June 2020. Quercetin and Vitamin C: An experimental, synergistic Therapy for the prevention and treatment of SARS-CoV-2 Related Disease (COVID-19) Immunol 11:1451. doi:10.3389/fimmu.2020.01451
2. Chen L, Li J et al Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure activity relationship studies reveal saliet pharmacophore features. Bioorg Med Chem (2006) 14:8295-306
3. Awad HM, Boersma MG, Boeren S, van der Woude H, van Zanden J, van Bladeren PJ, et al. Identification of o-quinone/quinone methide metabolites of quercetin in a cellular in vitro system. FEBS Lett. (2002) 520:30–34. doi: 10.1016/S0014-5793(02)02754-0
4. Boots AW, Li H, Schins RP, Duffin R, Heemskerk JW, Bast A, et al. The quercetin paradox. *Toxicol Appl Pharmacol.* (2007) 222:89–96. doi: 10.1016/j.taap.2007.04.004
5. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. *Eur J Pharmacol.* (2008) 585:325–37. doi: 10.1016/j.ejphar.2008.03.008
6. Askari G, Ghiasvand R, Feizi A, Ghanadian SM, Karimian J. The effect of quercetin supplementation on selected markers of inflammation and oxidative stress. *J Res Med Sci.* (2012) 17:637–41.
7. Boots AW, Kubben N, Haenen GR, Bast A. Oxidized quercetin reacts with thiols rather than with ascorbate: implication for quercetin supplementation. *Biochem Biophys Res Commun.* (2003) 308:560–5. doi: 10.1016/S0006-291X(03)01438-4
8. Bors W, Michel C, Schikora S. Interaction of flavonoids with ascorbate and determination of their univalent redox potentials: a pulse radiolysis study. *Free Radic Biol Med.* (1995) 19:45–52. doi: 10.1016/0891-5849(95)00011-L
9. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem Toxicol.* (2007) 45:2179–205. doi: 10.1016/j.fct.2007.05.015
10. Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology.* (1999) 54:960–3. doi: 10.1016/S0090-4295(99)00358-1
11. Ferry DR, Smith A, Malkhandi J, Fyfe DW, deTakats PG, Anderson D, et al. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. *Clin Cancer Res*. (1996) 2:659–68.

b. VITAMIN D

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Introduction

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

Mechanism of Action

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

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

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

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

As of August 14, 2020, there are 24 clinical trials registered in clinicaltrials.gov investigating the role of Vitamin D in COVID-19. Fifteen are ongoing randomized controlled trials, 7 are ongoing observational studies and 2 are completed observational studies.

Recommended Dose: [1,9]

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.[10]

Conclusion

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

REFERENCES

1. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC. National Academy Press; 2010.
2. Adams JS, Ren S, Liu PT et al. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J. Immunol 2009; 182: 4289–4295.
3. Laaksi, I. Vitamin D and respiratory infection in adults. Proc. Nutr. Soc. 2012; 71: 90–97.
4. Sharifi A, Vahedi H, Nedjat S et al. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: A randomized placebo-controlled trial. APMIS 2019; 127: 681–687.
5. Lemire, JM, Adams JS, Kermani-Ara V, et al. 1,25-Dihydroxyvitamin D3 suppresses human T helper/inducer lymphocyte activity in vitro. J. Immunol 1985; 134: 3032–3035.
6. Cantona MT, Snyder, L, Lin YD, et al. Vitamin D and 1,25(OH) 2D regulation of T cells. Nutrients 2015; 7: 3011–3021
7. Jeffery LE, Burke F, Mura M et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J. Immunol 2009; 183: 5458–5467
8. Mitchell F. Vitamin D and COVID-19: do deficient risk a person a poorer outcome? The Lancet Diabetes and Endocrinology Vol8, Issue7, July 01,2020
9. https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/
10. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008; 88:582S-6S.

c. 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]

Recommended Dose

Not yet established for COVID-19.

Adverse Effects

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

Conclusion

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

REFERENCES:

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

d. MELATONIN

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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.

REFERENCES

1. Reiter R.J., Ma.Q.Sharma R. Treatment of Ebola and other infectious diseases:melatonin “goes”viral” Melatonin Res.2020;3:43-57
2. Rui Zhang, Xuebin Wang,et.al. COVID-19:Melatonin as potential adjuvant treatment,Life Sci. 2020 Mar 23:117583
3. Ling,Y.,et al. MicroRNA-494 inhibition alleviates acute lung injury through Nrf2 signaling pathway via NQO1 in sepsis-associated acute respiratory disease syndrome. Life Sci. 2018;210:1-8.
4. Hardeland R. Melatonin and inflammation-story pf a double-edged blade. J. Pineal res. 2018;65:e12525
5. Ahmadi Z., et.al. Melatonin as a potential modulator of Nrf2. Fund. Clin. Pharmacol. 2020;34:11-19
6. Reiter RJ., et al. Treatment of Ebola and other infectious diseases: Melatonin ”goes viral” Melatonin Res. 2020;3:43-57
7. Wu X., et al. Melatonin alleviates radiation-induced lung injury via regulation of miR-30e/NLRP3 axis. Oxidative Med. Cell. Longev. 2019;2019:4087298.
8. Castillo, R., et al, Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series, Melatonin Research (Melatonin Res.) http://www.melatonin-research.net, 2020 Jun 3.
9. Foley HM, Steele AE. Adverse Events Associated With The Oral Administration Of Melatonin: A Critical Systematic Review Of Clinical Evidence. Complent Ther Med 2019. Feb; (42) 65-81 epub 2018 Nov 3.

e. PROBIOTICS

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Introduction

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

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

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

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

Mechanism of Action

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

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

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

Clinical Studies

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

Recommended Dose

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

Adverse Effects

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

Conclusion

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

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

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

REFERENCES:

1. Guidelines for the evaluation of probiotics in food: report of a joint FAO/ WHO working group on drafting guidelines for the evaluation of probiotics in food (accessed October 3, 2009) Available from: http:// www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf
2. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A Mechanisms of Action of Probiotics. Adv Nutr 2019 Jan 1;10 (suppl_1):S49-S66 doi: 10.1093/advances/nmy063
3. Zeng, Zhang et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomized controlled multicenter trial. Intensive Care Med. 2016; 42: 1018-1028
4. Morrow LE, Kollef MH , Casale TB Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med. 2010; 182: 1058-1064

5. Joyce W Y Mak, Francis K L Chan, *Siew C Ng siewchienng@cuhk.edu.hk , Probiotics and COVID-19: one size does not at all , Lancet, Gastroenterology and Hepatology , April 24,2020, https://doi.org/10.1016/S2468-1253(20)30122-9

f. OMEGA 3 FATTY ACID AND DHA

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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.

REFERENCES:

1. Gutierrez S, Svahn S, ohansson ME. Effects of omega-3 fatty acids on immune cells. Int J Mol Sci.2019 Oct; 20(20):5028
2. Fenton J, Hord N, Ghsh S, Gurzell E.Immunomodulation by dietary long chain omega-3 fatty acid and the potential for adverse health outcomes.Prostaglandins, Leukotrienes and Essential Fatty Acids. 2013 Nov-Dec;89(6):379-390.
3. Brand K, Page S, Rogler G, Bartsch A, Brandl R, Knuechel R, Page M, Kaltschmidt C, Baeuerle PA, Neumeier D. Activated transcription factor nuclear factor-kappa B is present in the atherosclerotic lesion. J Clin Invest. 1996;97:1715–1722.
4. Bousserouel S, Brouillet A, Bereziat G, Raymondjean M, Andreani M. Different effects of n-6 and n-3 polyunsaturated fatty acids on the activation of rat smooth muscle cells by interleukin-1 beta. Journal of lipid research. 2003;44:601–611.
5. De Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. The American journal of clinical nutrition. 2000;71:213S–223S.
6. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G, Hwang DH. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res. 2003;44:479–486.
7. Chang H.Y., Lee H.N., Kim W., Surh Y.J. Docosahexaenoic acid induces M2 macrophage polarization through peroxisome proliferator-activated receptor gamma activation. Life Sci. 2015;120:39–47. doi: 10.1016/j.lfs.2014.10.014.
8. Svahn S.L., Ulleryd M.A., Grahnemo L., Stahlman M., Boren J., Nilsson S., Jansson J.O., Johansson M.E. Dietary Omega-3 Fatty Acids Increase Survival and Decrease Bacterial Load in Mice Subjected to Staphylococcus aureus-Induced Sepsis. Infect Immun. 2016;84:1205–1213. doi: 10.1128/IAI.01391-15.
9. Jin M., Park S., Park B.K., Choi J.J., Yoon S.J., Yang M., Pyo M.Y. Eicosapentaenoic Acid and Docosahexaenoic Acid Suppress Th2 Cytokine Expression in RBL-2H3 Basophilic Leukemia Cells. J. Med. Food. 2014;17:198–205. doi: 10.1089/jmf.2013.2935.
10. Latif M.A., Abdul-Hamid M., Galaly S.R. Effect of diethylcarbamazine citrate and omega-3 fatty acids on trimellitic anhydride-induced rat skin allergy. Asian Pac. J. Allergy Immunol. 2015;33:33–41. doi: 10.12932/AP0499.33.1.2015.
11. Onodera T., Fukuhara A., Shin J., Hayakawa T., Otsuki M., Shimomura I. Eicosapentaenoic acid and 5-HEPE enhance macrophage-mediated Treg induction in mice. Sci. Rep. 2017;7:4560. doi: 10.1038/s41598-017-04474-2.
12. Teague H., Fhaner C.J., Harris M., Duriancik D.M., Reid G.E., Shaikh S.R. n-3 PUFAs enhance the frequency of murine B-cell subsets and restore the impairment of antibody production to a T-independent antigen in obesity. J. Lipid Res. 2013;54:3130–3138. doi: 10.1194/jlr.M042457.
13. Gammone MA, Riccioni G, Parrinello G, D'Orazio N. Omega-3 polyunsaturated fatty acid: Benefits and endpoints in sport. Nutrients.2019 Jan;11(10:46.
14. Gammone M.A., D'Orazio N. Anti-obesity activity of the marine carotenoid fucoxanthin. Mar. Drugs. 2015;13:2196–2214. doi: 10.3390/md13042196.

NEW IMMUNOMODULATORS REVIEWED FOR THE 3RD VERSION

1. ANTI-COAGULANTS (HEPARIN AND ITS DERIVATIVES)

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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 cytokine as seen in Figure 4.[17,18,19]

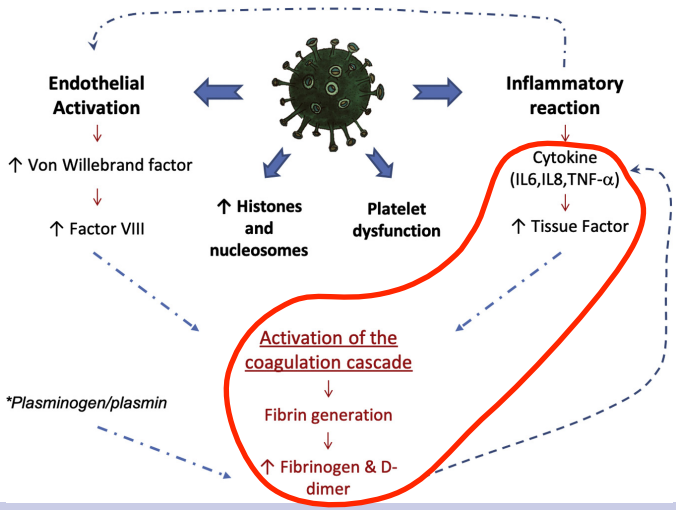

Figure 4. Mechanisms of coagulation impairment in COVID-19 infection. Area encircled shows the relationship between coagulation by-products and augmentation of the inflammatory response. (Adapted from Constanzo, et al)

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

According to a search done at clinicaltrials.gov site, only 3 (2 observational, 1 interventional, no RCT's) studies on heparin and its derivatives have been completed as of this writing but results have not been reported yet. There are at least 9 other studies that are in various stages of development.

Recommended Dose

The International Society of Thrombosis and Haemostasis (ISTH) has also endorsed the guidelines of the Journal of American College of Cardiology which recommends that hospitalized COVID19 patients with respiratory failure, comorbid conditions (cancer, heart failure), bedridden and receiving intensive care should receive pharmacological venous thromboembolism prophylaxis unless with contraindications. No specific doses were given.[37]

In the Philippines, the Philippine Society of Vascular Medicine (PSVM) has suggested the initiation of anticoagulation prophylaxis if any the following are present in COVID 19 patients:[38]

a) ISTH criteria [39,40]: D-dimer > 2 micrograms/ml ± prolonged protime ± platelet <100x 10^{9}/L
b) Bleeding risk by Padua Prediction score for venous thromboembolism ≥ 4 [41]
c) Sepsis-induced coagulopathy (SIC) >4[42]
d) Critically ill (admission to ICU requiring mechanical ventilation or FiO2 of 60% or higher)[41]

		Enoxaparin	Unfractionated Heparin
Patient's Weight	<80 kg 80-120 kg >120 kg	40 mg SC OD 60 mg SC OD 80 mg SC OD	5,000 u SC Q8H or Q12H (for all weight categories)
Creatinine Clearance (CrCl)	≥ 30 ml/min 15-29 ml/min <15 ml/min	As above (according to patient's weight 20 mg SC Not indicated	5,000 u SC Q8H or Q12H 5,000 u SC Q8H or Q12H 5,000 u SC Q12H

PSVM recommended doses:

Contraindications for heparin prophylaxis include:[39]
(1) Platelet <25 x $10^{9/}$L
(2) Active bleeding

The PSVM also advises that anticoagulation should be discontinued when:
(1) Platelet count ≤ 20 x 10^9/L without bleeding[39]
(2) Platelet count ≤ 50 x 10^9/L with PT ratio ≥ 1.5[39]
(3) General ISTH bleeding criteria:
   a. Fatal bleeding, and/or
   b. Bleeding in a critical area or organ (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or
   c. Bleeding causing a fall in hemoglobin level of 2g/dl (1.24 mmol/L) or more or leading to transfusion of two or more units of whole blood or red cells

Adverse Effects

There is a 10-15% risk of significant bleeding in heparin use. [43,44] 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.[45] However, this is not seen in the use of fondaparinux.

Conclusion

Although heparin has many immunomodulatory effects, its exact mechanism in improving outcomes for COVID-19 patients has yet to be elucidated. However, its potential in providing prophylaxis of thromboembolism as a consequence of COVID-19 should be considered.

REFERENCES:

1. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. Circulation 2001;103:1718-20.

2. Marik, PE, Andrews L, Maini B. The incidence of deep venous thrombosis in ICU patients. Chest 1997;**111**, 661–664
3. Song J, Wang, G, Zhang W. et al. Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Military Med Res 2020; **7,** 19. Available from https://doi.org/10.1186/s40779-020-00247-7
4. Merrill, JT, Erkan, D, Winakur, J. *et al.* Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. Nat Rev Rheumatol 2020. Available from: https://doi.org/10.1038/s41584-020-0474-5
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–847. Available from: https://doi.org/10.1111/jth.14768
6. KlokFA,KruipMJHA,vanderMeerNJM,etal.IncidenceofthromboticcomplicationsincriticallyillICUpatients with COVID-19. Thromb Res. 2020. doi:10.1016/j.thromres.2020.04.013
7. Llitjos JF, Leclerc M, Chochois C, etal. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. Published online April 22, 2020. Available from: doi:10.1111/jth.14869
8. Nahum J, Morichau-Beauchant T, Daviaud F, et al. Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). JAMA Netw Open. 2020;3(5):e2010478. Available from: doi:10.1001/jamanetworkopen.2020.10478
9. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. Available from: https:// doi.org/10.1001/jamainternmed.2020.0994.
10. Brinkhous K, Smith H, Warner E, Seegers W. The inhibition of blood clotting: An unidentified substance which acts in conjunction with heparin to prevent the conversion of prothrombin into thrombin. Am. J. Physiol 1939;125:683–687.
11. Lindahl U, Bäckström G, Höök M et al. Structure of the antithrombin-binding site in heparin. Proc. Natl. Acad. Sci. USA. 1979;76:3198–3202. Available from: doi: 10.1073/pnas.76.7.3198.
12. Lane DA, Denton J, Flynn AM et al. Anticoagulant activities of heparin oligosaccharides and their neutralization by platelet Ffactor 4. Biochem. J. 1984;218:725–732. Available from: doi: 10.1042/bj2180725.
13. Oosta GM, Gardner WT, Beeler DL et al. Multiple functional domains of the heparin molecule. Proc. Natl. Acad. Sci. USA. 1981;78:829–833. Avaialble from: doi: 10.1073/pnas.78.2.829.
14. Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-height Heparin. Thromb. Haemost. 2008;99:807–818. Available from: doi: 10.1160/TH08-01-0032.
15. Shaughnessy SG, Young E, Deschamps P, Hirsh J. The effects of low molecular weight and standard heparin on calcium loss from fetal rat calvaria. Blood. 1995;86:1368–1373.
16. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, present, and future. Pharmaceuticals (Basel). 2016;9(3):38. Availlble from: doi:10.3390/ph9030038
17. Li J, Hara H, Wang Y, Esmon C, Cooper DK, Iwase H. Evidence for the important role of in"ammation in xeno- transplantation. J Infamm 2019;16:10.
18. Robson SC, Shephard EG, Kirsch RE. Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1 beta, IL-6 and plasminogen activator inhibitors from monocytes in vitro. Br J Haematol 1994;86: 322-6.
19. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinfammatory cytokine levels and outcomes in critically ill patients. Chest 2002;121:1262-8.
20. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-inflammatory effects of heparin and its derivatives: A systematic review. Adv Pharmacol Sci. 2015;2015:507151. Available from: doi:10.1155/2015/507151
21. Young E. The Anti-Inflammatory Effects of Heparin and Related Compounds. Thromb. Res. 2008;122:743–752.Available from: doi: 10.1016/j.thromres.2006.10.026.
22. Li JP, Vlodavsky I. Heparin, heparan sulfate and heparanase in inflammatory reactions. Thromb Haemost. 2009;102(5):823-828
23. Nelson RM., Cecconi O, Roberts WG, et al. Heparin oligosaccharides bind L- and P-Selectin and inhibit acute inflammation. Blood. 1993;82:3253–3258.

24. Ma J, Bai J. Protective effects of heparin on endothelial cells in sepsis. Int J Clin Exp Med 2015;8:5547-52.
25. Thourani VH, Brar SS, Kennedy TP, et al. Nonanticoagulant heparin inhibits NF-κB activation and attenuates myocardial reperfusion injury. Am. J. Physiol. Heart Circ. Physiol. 2000;278:H2084–H2093.
26. Esmon CT. Targeting factor Xa and thrombin: impact on coagulation and beyond. Thromb Haemost. 2014;111(4):625-633
27. Ritis K, et al. A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. JImmunol. 2006;177(7):4794–4802.
28. Foley JH, Conway EM. Cross talk pathways between coagulation and inflammation. Circ Res. 2016;118(9):1392–1408.
29. Yan Zhang, Meng Xiao, Shulan Zhang et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19 Case report. N Engl J Med 2020; 382:e38
30. (31) Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31(4):256-263
31. Iba T, Hashiguchi N, Nagaoka I, et al. Heparins attenuated histone-mediated cytotoxicity in vitro and improved the survival in a rat model of histone- induced organ dysfunction. Intensive Care Med Exp 2015;3:36.
32. Zhu C, Liang Y, Li X et al. Unfractionated heparin attenuates histone-mediated cytotoxicity in vitro and prevents intestinal microcirculatory dysfunction in histone- infused rats. J Trauma Acute Care Surg 2019;87:614-22.
33. Milewska A, Nowak P, Owczarek K, et al. Entry of human coronavirus NL63 into the cell. J Virol 2018. 92: e01933-17. Avialble from: doi:10.1128/JVI.01933-17.
34. Lang J, Yang N, Deng J, et al. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparan sulfate proteoglycans. PLoS One 6 2011: e23710. Available from: doi:10.1371/journal.pone. 0023710.
35. Hippensteel JA, LaRiviere WB, Colbert JF et al.. Heparin as a therapy for COVID-19: current evidence and future possibilities. Am J Physiol Lung Cell Mol Physiol. 2020;319(2):L211-L217. Avaialble from: doi:10.1152/ajplung.00199.2020
36. Kim SY, Jin W, Sood A, et al. Glycosaminoglycan binding motif at S1/S2 proteolytic cleavage site on spike glycoprotein may facilitate novel coronavirus (SARS-CoV-2) host cell entry. (Preprint). *bioRxiv* 2020. Available from: doi:10.1101/2020.04.14.041459.
37. Bikdeli, et al., COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-Up. J Am Coll Cardiol. 2020 Jun, 75 (23) 2950-2973.
38. Philippine Society of Vascular Medicine. PSVM Interim Guidelines on Vascular Procedures and Treatment Interventions During COVID-19 Pandemic. https://www.pcp.org.ph. August 2020
39. Thachill J, Tang N, Gando S et al. International Society of Thrombosis and Haemostasis (ISTH) interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020. 18: 1023-1026. Available from doi:10.1111/jth.14810
40. Yao Y, Cao J, Wang Q et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J intensive care 2020. **8,** 49 Available from: https://doi.org/10.1186/s40560-020-00466-z
41. Jin-fu Xu, Lan Wang, Lan Zhao et al. Risk assessment of venous thromboembolism and bleeding in COVID-19 patients. PREPRINT (Version 1) (24 March 2020) Available from Research Square https://doi.org/10.21203/rs.3.rs-18340/v1
42. Tang N, Bai H, Chen X et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. Available from http://doi:10.1111/jth.14817
43. Cossette B, Pelletier MÈ, Carrier N et al. Evaluation of bleeding risk in patients exposed to therapeutic unfractionated or low-molecular-weight heparin: a cohort study in the context of quality improvement initiative. Ann Pharmacother 2010. 44: 994–1002. Avaialble from: doi:10.1345/aph.1M615.
44. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood 1991. 78: 2337–2343. Avaialble from: doi:10.1182/blood.V78.9.2337.2337.

45. Arepally GM. Heparin-induced thrombocytopenia. Blood 2017. 129: 2864– 2872. Available from: doi:10.1182/blood-2016-11-709873.

2. ANTIHISTAMINES

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Introduction

Antihistamines have been widely used as treatment of different allergic conditions such as allergic rhinitis, allergic conjunctivitis and urticaria. [1] Recently, 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].

Mechanism of Action

H1-antihistamines downregulate allergic inflammation directly through the H1-receptor. They interfere with histamine action at H1-receptors on sensory neurons and small blood vessels. Through the inhibition of 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]

Clinical Studies

There are no published clinical trials examining the use of antihistamines in COVID-19. However, antihistamines combined with low-dose systemic steroids can play a role in the control of COVID-19 related urticarial rashes. [3,4]

Conclusion

There have been no studies examining the use of antihistamines in COVID-19. Clinical trials would be required to establish whether these drugs may be used for treatment of this disease.

REFERENCES:

1. Simons FE, Simons K. Histamine and H1-antihistamines: Celebrating a century of progress. J Allergy Clin Immunol 2011; 128: 1139-50.
2. Raymond M, Ching-A-Sue G, Van Hecke O. Mast cell stabilizers, leukotriene antagonists and antihistamines: a rapid review of the evidence for their use in COVID- 19. Center for Evidence-Based Medicine; 2020.
3. Mohammed Shanshal (2020) Low-dose systemic steroids, an emerging therapeutic option for COVID-19 related urticaria, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2020.1795062
4. Tang K, Wang Y, Zhang H, Zheng Q, Fang R, Sun Q. Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review [published online ahead of print, 2020 May 7]. *Dermatol Ther*. 2020;e13528. doi:10.1111/dth.13528

3. BETA-GLUCAN

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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]

REFERENCES:

1. Akramiene D, Kondrotas A, Didziapetriene J, Kevelaitis E. Effects of beta-glucans on the immune system. *Medicina.* (2007) 43:597–606. doi: 10.3390/medicina43080076
2. Kaur, R., Sharma, M., Ji D, Xu M, Agyei, D. 2020. Structural features, modification, and functionalities of beta-glucan. Fibers. 8(1):1. https://doi.org/https://doi.org/10.3390/ fib8010001.
3. McCarty, M.F., Di Nicolantonio, J.J., 2020. Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus. Prog. Cardiovasc. Dis. https://doi.org/10.1016/j.pcad.202.02.007.
4. EJ. Murphy, et. al. β-Glucan extracts from the same edible shiitake mushroom *Lentinus edodes* produce differential in-vitro immunomodulatory and pulmonary cytoprotective effects — Implications for coronavirus disease (COVID-19) immunotherapies. Science of the Total Environment 732 (2020)139330. https://doi.org/10.1016/j.scitotenv.2020.139330.
5. Rao K-S, Suryaprakash V, Senthilkumar R, Preethy S, Katoh S, Ikewaki N and Abraham SJK (2020) Role of Immune Dysregulation in Increased Mortality Among a Specific Subset of COVID-19 Patients and Immune-Enhancement Strategies for Combatting Through Nutritional Supplements. Front. Immunol. 11:1548. doi: 10.3389/fimmu.2020.01548
6. M. Novak & V. Vetvicka (2008) β-Glucans, History, and the Present: Immunomodulatory Aspects and Mechanisms of Action, Journal of Immunotoxicology, 5:1, 47-57, DOI: 10.1080/15476910802019045
7. Petravic-Tominac, Vlatka, et.al. Biological effects of Yeast b-Glucans. Agriculturae Conspectus Scientificus | Vol. 75 (2010) No. 4 (149-158).
8. Ikewaki N, Fujii N, Onaka T, Ikewaki S, Inoko H. Immunological actions of Sophy beta-glucan (beta-1,3-1,6 glucan), currently available commercially as a health food supplement. *Microbiol Immunol*. (2007) 51:861–73. doi: 10.1111/j.1348-0421.2007.tb03982.x

4. H2 RECEPTOR BLOCKERS (FAMOTIDINE)

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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

1. Anti-viral 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) as well as two other proteases involved in SARS-CoV2 replication, the viral PLpro and human host Tmprss2.[3]

2. 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 mast cell 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

Currently ongoing in the United States is a multi-site, randomized, double-blind comparative clinical trial on the safety and efficacy of standard of care (SOC) plus Famotidine versus SOC plus placebo for the treatment of hospitalized patients with COVID 19. (Appendix 13)

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. Three hundred forty (340) (21%) patients met the study composite outcome of death or intubation. 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 (PPIs), which also suppress gastric acid, were not associated with reduced risk for death or

intubation.[5]

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-hospitalised 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.[6]

However, the findings of a preprint of a territory-wide retrospective cohort study (done in all COVID-19 patients reported 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 as defined. Twenty three (2.4%) and four (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). [7]

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-hospitalised patients with COVID-19 was 60 to 240 mg PO for a median of 11 days (range: 5-21 days).[6]

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.[8] 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.[9]

Conclusion

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

REFERENCES:

1. Wallace JL, Sharkey KA. Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 11093-22.
2. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods [published online ahead of print, 2020 Feb 27]. Acta Pharm Sin B. 2020;10(5):766-788. doi:10.1016/j.apsb.2020.02.008
3. Ortega JT, Serrano ML, Jastrzebska B. Class A G Protein-Coupled Receptor Antagonist Famotidine as a Therapeutic Alternative Against SARS-CoV2: An In Silico Analysis. Biomolecules. 2020;10(6):954. Published 2020 Jun 24. doi:10.3390/biom10060954
4. Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. Preprint. *Res Sq*. 2020;rs.3.rs-30934. Published 2020 Jun 22. doi:10.21203/rs.3.rs-30934/v2
5. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study [published online ahead of print, 2020 May 22]. Gastroenterology. 2020;S0016-5085(20)34706-5. doi:10.1053/j.gastro.2020.05.053
6. Janowitz T, Gablenz E, Pattinson D, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series [published online ahead of print, 2020 Jun 4]. Gut. 2020;gutjnl-2020-321852. doi:10.1136/gutjnl-2020-321852
7. Cheung KS, Hung IF, Leung WK, Association between famotidine use and COVID-19 severity in Hong Kong: a territory-wide study, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.098 .
8. Howden CW, Tytgat GN. The tolerability and safety profile of famotidine. Clin Ther. 1996;18(1):36-35. doi:10.1016/s0149-2918(96)80177-9
9. Lee KW, Kayser SR, Hongo RH, Tseng ZH, Scheinman MM. Famotidine and long QT syndrome. Am J Cardiol. 2004;93(10):1325-1327.doi:10.1016/j.amjcard.2004.02.025

5. 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 (PI^{pro}) is an enzyme necessary for viral maturation and survival against the host's interferon reponse. MPA has been found to inhibit MERS-CoV PI^{pro} activity. However, the same study demonstrated that MPA had no effect on SARS-CoV PI^{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.

REFERENCES:

1. National Center for Biotechnology Information [Internet]. PubChem Database: 2005 March 26. Mycophenolic acid. [Updated 2020 July 12]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Mycophenolic-acid (accessed on 2020 July 14)
2. Katzung, BG. *Basic and Clinical Pharmacology*. 14th ed. New York: McGraw-Hill Education; 2018. p. 666, 987.
3. Geevasinga N, Wallman L, Katelaris CH. Mycophenolate Mofetil; A Review of Indications and Use in a Large Tertiary Hospital. *Iran J Allergy Asthma Immunol*. 4(4):159-166. Available from: https://ijaai.tums.ac.ir/index.php/ijaai/article/view/116 (accessed on 2020 July 14)
4. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect*. 2013;67(6):606-616. doi:10.1016/j.jinf.2013.09.029
5. Hart BJ, Dyall J, Postnikova E, et al. Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol*. 2014; 95(Pt 3):571-577. doi:10.1099/vir.0.061911-0
6. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res*. 2015;115:9-16. doi:10.1016/j.antiviral.2014.12.011
7. Kato F, Matsuyama S, Kawase M, et al. Antiviral activities of mycophenolic acid and IMD-0354 against SARS-CoV-2 [published online ahead of print, 2020 Jun 24]. *Microbiol Immunol*. 2020;10.1111/1348-0421.12828. doi:10.1111/1348-0421.12828
8. Heinschink A, Raab M, Daxecker H, et al. In vitro effects of mycophenolic acid on cell cycle and activation of human lymphocytes. *Clin Chim Acta*. 2000;300(1-2):23-28. doi:10.1016/s0009-8981(00)00297-7
9. Blaheta RA, Leckel K, Wittig B, et al. Mycophenolate mofetil impairs transendothelial migration of allogeneic CD4 and CD8 T-cells. *Transplant Proc*. 1999;31(1-2):1250-1252. doi:10.1016/s0041-1345(98)01984-8
10. Lee J, Kim MS, Kim EY, et al. Mycophenolate mofetil promotes down-regulation of expanded B cells and production of TNF-alpha in an experimental murine model of colitis. *Cytokine*. 2008;44(1):49-56. doi:10.1016/j.cyto.2008.06.006
11. Karnell JL, Karnell FG 3rd, Stephens GL, et al. Mycophenolic acid differentially impacts B cell function depending on the stage of differentiation. *J Immunol*. 2011 Oct 1;187(7):3603-12. doi: 10.4049/jimmunol.1003319
12. Al Ghamdi M, Alghamdi KM, Ghandoora Y, et al. Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia. *BMC Infect Dis*. 2016;16:174. Published 2016 Apr 21. doi:10.1186/s12879-016-1492-4
13. Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Mycophenolate. [Updated 2020 Feb 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548945/ (accessed on 2020 July 14).

6. VIRGIN COCONUT OIL (LAURIC ACID)

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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.

REFERENCES:

1. Dayrit, F. and M. Newport. The Potential of Coconut Oil and its Derivatives as Effective and Safe Antiviral Agents Against the Novel Coronavirus (nCoV-2019) https://www.icp.org.ph/2020/01/the-potential-of-coconut-oil-and-its-derivatives-as-effective-and-safe-antiviral-agents-against-the-novel-coronavirus-ncov-2019/ 2020 Jan.
2. Piret, J., A. Desormeaux, MG Bergerson. Sodium Lauryl Sulfate, a microbicide effective against enveloped and non-enveloped virus. Current Drug Targets. 2002, 3:17-30.
3. Hierholzer, J., J. Kalara. In vitro effects of monolaurin compounds on enveloped RNA and DNA viruses. Journal of Food Safety. (4):1 - 12. 1981 October.
4. Bartolotta, S., C.C. Garcıa, N. A. Candurra, and E. B. Damonte. Effects of fatty acids on arenavirus replication: Inhibition of virus production by lauric acid. Arch Virol. 146:777-790. 2001
5. Thormar. H. et al. Inactivatioin of enveloped viruses and killing of cells by fatty acids and monoglycerides. Antimicrobial Agents and Chemotherapy 31(1): 27-31. 1987 January.
6. Horning, B. et al. Lauric acid inhibits the maturation of vesicular stomatitis virus (VSV). J General Virology (75): 353-361. 1994
7. Widhiarta, DK. Virgin coconut oil for HIV positive people. Cord 34(1). 2016
8. Wallace FA, Miles EA, Evans C, Stock TE, et al. Dietary fatty acids Influence the production of Th1 but not Th2 type cytokines. J Leukoc Biol. 69(3): 449-57. 2001 Mar.

CONCLUDING REMARKS

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

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

As we state that some of the immunomodulators have not yet proven to be effective, with the results of ongoing studies we are hopeful that we get positive answers from these researches. Presently many drug researches are ongoing and their results will validate which immunomodulators will best be given for patients who are afflicted with this disease.

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

We present our third version dated September 20, 2020.

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- All the health care workers who continue risk their lives so that we may continue to learn and improve.

APPENDICES

Appendix 1. List of Authors and their Academic Position or Hospital Affiliation
Appendix 2. Availability of the Immunomodulators in the Philippines

Tables of Studies of the aforementioned Immunomodulators for COVID-19
Appendix 3.

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- **Pauline Florence R. Santos Estrella, MD**
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- **Jennifer Serrano-Flores, MD**
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- **Frances M. Tan, MD**
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- **Felicia Racquel S. Tayag, MD**
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- **Maria Rowena B. Valerio, MD**
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- **Beatrice S. Vicente Pascual, MD**
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- **Venjilyn S. Villaver, MD**
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- **Celine N. Yapjuangco, MD**
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- **Cynthia Purificacion Ybiernas-Gallinero, MD**
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2. 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	
Anti-IL1		Anakinra
Anti-IL6	Tocilizumab	
Anti-malarial agents	Hydroxychloroquine Chloroquine	
Anti-viral Agents	Lopinavir/Ritonavir Remdesivir Favipiravir	Ribavirin Umifenovir (Arbidol)
Calcineurin Inhibitors	Cyclosporine A Tacrolimus	
Corticosteroid	Methylprednisolone	
H2 Blocker	Famotidine	
Interferons	IFN α, IFN β	
JAK 1,2 inhibitors		Baricitinib
Macrolide	Azithromycin	

3. TABLES OF PUBLISHED STUDIES