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Medical Bulletin

EXCEL Division of Blue Cross Laboratories

Pathophysiology of COVID-19 and Role of Azithromycin (Azibest)

INFECTION

The SARS-CoV-2 virus, enters the body – generally through the mouth or nose. From there, the virus makes its way down into the air sacs inside your lungs, known as alveoli. Once in the alveoli, the virus uses its distinctive spike proteins to "hijack" cells. The primary genetic programming of any virus is to make copies of itself, and COVID-19 is no exception.

Once the RNA of the virus has entered a cell, new copies are made and the cell is killed in the process, releasing new viruses to infect neighbouring cells in the alveolus.

IMMUNE RESPONSE

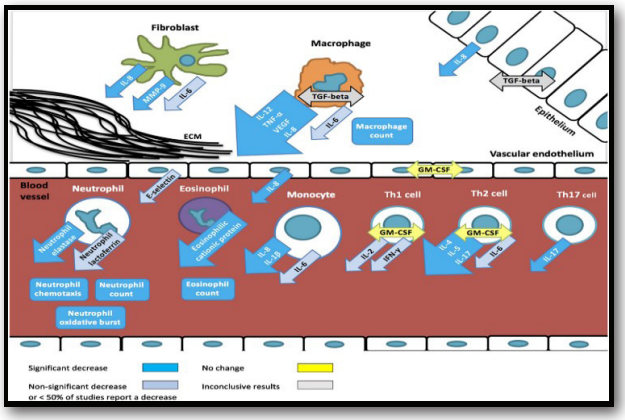
The process of hijacking cells to reproduce causes inflammation in the lungs, which triggers an immune response. As this process unfolds, fluid begins to accumulate in the alveoli, causing a dry cough and making breathing difficult.

SEVERE SYMPTOMS

In 15-20% cases, the immune system's response to inflammation in the lungs can cause what's known as a "cytokine storm". This response can cause more damage to the body's own cells than to the virus it's trying to defeat, and can rapidly deteriorate.

HYPOTHESIS OF AZITHROMYCIN FOR COVID-19 THERAPY

Like other macrolides, apart from its antimicrobial properties, azithromycin also exhibits anti-inflammatory, immunomodulatory, and anti-proliferative effects, as well as an autophagy effect by leading to apoptotic cell death.



Anti-inflammatory properties of macrolides

IMMUNO-MODULATION/ANTI-INFLAMMATORY

Cytokines and chemokines are key regulators of the inflammatory response, with both proinflammatory (TNF-α , granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin-1 [IL-1], IL-6, IL-8, and IFN- Y) and anti-inflammatory (IL-10) effects.

Macrolides like azithromycin appear to decrease the production of proinflammatory cytokines that are detrimental to the host and hence may prevent a hyperimmune response to the virus.

Neutrophil Lymphocyte Ratio (NLR)

NLR reflects the severity of inflammation in the body, and has been proposed as a new biomarker for systemic inflammation.

Several studies have described the clinical characteristics of patients with SARS-CoV-2 infected pneumonia, indicating severe patients tend to have higher neutrophil to lymphocyte ratio (NLR).

It is now recognised as an independent risk factor of the in-hospital mortality for COVID-19 patients. The inflammatory response could stimulate the production of neutrophils and speed up the apoptosis of lymphocytes.

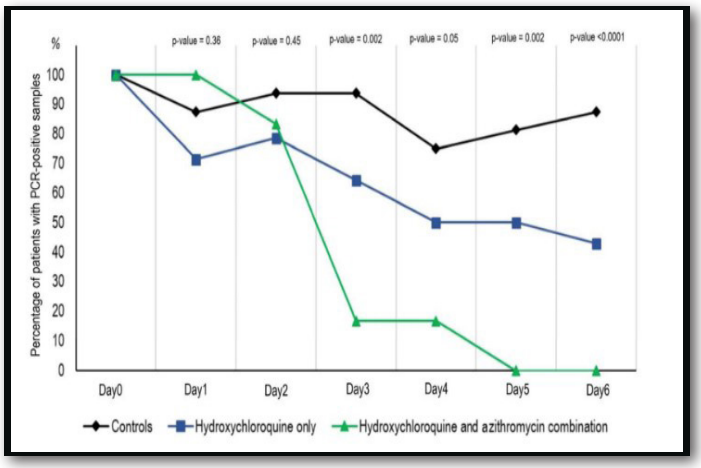
Azithromycin has shown to significantly reduce the levels of neutrophils and increase the proliferative response of lymphocytes, thus significantly improve the NLR.

Hence, azithromycin is being investigated as adjunctive therapy based on anti-inflammatory or immuno-modulatory effects when used in patients with some viral infections, including COVID-19.

CLINICAL STUDIES :

In a study conducted in France on 1061 COVID-19 patients, treated for 3 days with HCQ-Azithromycin combination, it was observed that HCQ-Azithromycin combination, when started immediately after diagnosis, was a safe and efficient treatment for COVID-19, with a mortality rate of 0.5%, in elderly patients.

In another French study, confirmed COVID-19 patients were treated with HCQ and azithromycin was added depending on their clinical presentation. It was observed that HCQ treatment was significantly associated with the viral load reduction/disappearance in COVID-19 patients and its effect was reinforced by azithromycin.



Source: https://www.researchgate.net/publication/340448998_Azithromycin_promising_medicine_for_COVID_19_in_early_stage_by_effecting_on_mTOR immune_system

COMPARING PROPANOL {Propan-2-ol & Propan-1-ol} MULTICIDAL VS ETHANOL HAND RUB DISINFECTANTS

Higher Concentration of Alcohol – Lesser Water Percentage – Lesser Efficacy

Alcohol solutions containing 60–80% alcohol are most effective, with higher concentrations being less potent.

This paradox results from the fact that proteins are not denatured easily in the absence of water.

Isopropyl alcohol is considered more efficacious against bacteria.

Conclusion:

Isopropyl alcohol (45%) and n-propanol (30%) have more percentage of water compared to commonly used ethanol preparations (> 60%, 85%). Thus, combination therapy of n-propanol and isopropanol is more effective than ethanol.

Higher concentrations of alcohol evaporate more quickly than lower concentrations

Rapid evaporation limits the time (contact time) that they can exert their disinfectant effect.

Research conducted at 3 and 5 min contact time between ethanol and isopropanol hand rub, Isopropanol caused better result in decreasing the skin flora.

75% propanol (mixture of 45% propan-2-ol and 30% propan-1-ol) significantly exceeded the European/U.S efficacy requirements for surgical hand antisepsis with an application time of 1.5 min as against 2 min for ethanol.

Conclusion:

Because of its higher concentration ethanol (>65%, 80%) evaporates too quickly as compared to isopropyl alcohol (45%) and n-propanol (30%), leading to lesser contact time and thereby lesser efficacy.

More Lipophilicity – More Efficacy against Enveloped Viruses

Enveloped viruses (lipophilic) are more susceptible to the isopropanol-based formulations as compared to the ethanol-based formulations. Further, the more carbon atoms in isopropanol make it more lipophilic and offer higher virucidal activities against the lipophilic viruses.

SARS CoV, RSVs, Zika, Ebola, Influenza, HIV, Hepatitis are few examples of enveloped viruses.

Ethanol has the disadvantage of high flammability as compared to Isopropanol.

Under Biocidal Product Regulation (BPR) for use in hand disinfection, propan-2-ol & propan-1-ol are approved in EU however Ethanol is still under evaluation.

Summary:
More efficacious bactericidal activity.
More effective against the enveloped viruses because of lipophilicity.
Exceeds European / US efficacy requirements for surgical hand wash at 1.5 min.

Source:Mitra Z et.al;Iran J Nurs Midwifery Res. 2015 Mar-Apr; 20(2): 221–225.Kampf G. Journal of Hospital Infection 98 (2018) 331e338.;Siddharta A, et al. The Journal of Infectious Diseases 2017; 215: 902–906.; https://echa.europa.eu/information-on-chemicals/biocidal-active-substances/-/disas /substance/100.000.601

Methylcobalamin (Mego-XL Caps/Inj) & COVID-19

HOW DOES METHYLCOBALAMIN WORK?

METHYLCOBALAMIN

It plays vital roles in the body and is also found to have some antiviral effects.

Immune Function: Vitamin B12 is known to maintain a healthy gut microbiome and thus help in the functioning of the immune system.

Viral Replication: Like other members of this family, the SARS CoV-2 virus possesses a positive-sense single-stranded RNA genome. This genome encodes for a particular protein called the **nsp12 protein**, which houses the RNA-dependent-RNA polymerase (RdRP) activity, which is responsible for the replication of the viral genome.

Vitamin B12 (methylcobalamin) is suggested to bind to the active site of the nsp12 protein with significant affinity suggesting that methylcobalamin form of vitamin B12 may serve as an effective inhibitor of the nsp12 protein and preventing replication of the virus.

A cohort study in Singapore has found that the combination of vitamin D(1000IU), magnesium(150 mg)and vitamin B12 (500 mcg)could reduce the rate of progression in older patients with Covid-19 as compared to patients who did not receive the same.

Vitamin B12 Metabolism: Another hypothesis suggests that SARS CoV-2 virus interferes with the cobalamin metabolism, causing symptoms of cobalamin deficiency. This is plausible to infer, because there are symptoms of vitamin B12 deficiency that are similar to those of COVID-19.
These symptoms include increase oxidative stress, homocysteine concentration, activation of the coagulation cascade, thrombocytopenia, elevated lactate dehydrogenase (LDH), low reticulocyte count, intravascular coagulation thrombosis, vasoconstriction, renal and pulmonary vasculopathies, which can result in respiratory, gastrointestinal and central nervous system disorders.
Research has shown that treatment with vitamin B12, especially methylcobalamin, would reduce Covid's damage to infected patients. Hence it is suggested that methylcobalamin (vitamin B12) may serve as an attenuator to COVID-19 symptoms.

CONCLUSION

The data thus suggests that Methylcobalamin and its combination could be used as an adjunct therapy in preventing the severity of Covid-19 infections. Also, based on the suggested mechanisms of Vitamin B12, especially methylcobalamin supplementation can prove to be effective in reducing the viral load as well as attenuate Covid-19 symptoms.

Sources:https://www.eatthis.com/vitamin-b12-deficiency-coronavirus/.Dai Q et al. The American Journal of Clinical Nutrition 2018; 108(6): 1249-1258. https://www.rcb.res.in/upload/deepaktnair_nsp12%20(1).pdf https://www.researchgate.net/publication/342281788_Can_vitamin_B12_be_an_adjuvant_to_COVID-19_treatment.

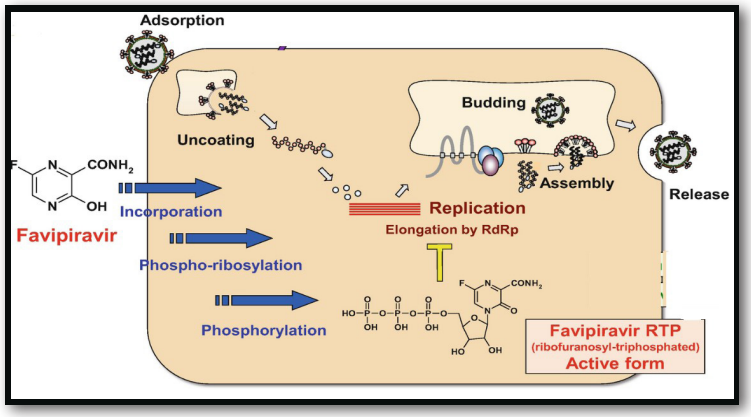
FAVIPIRAVIR - A Broad Spectrum Antiviral Agent

Favipiravir is a broad spectrum antiviral agent & is effective against all types of RNA viruses.
One of the most promising targets for coronaviruses is the RNA-dependent RNA polymerase (RdRP), which is a crucial enzyme in the life cycle of SARS-CoV-2 and Favipiravir inhibits this enzyme & halts the viral replication.
Favipiravir is a pro-drug of a purine nucleotide, favipiravir ribofuranosyl-5'-triphosphate and is the first orally administered drug approved for the treatment of COVID-19 in India.

Pharmacodynamics:
Favipiravir undergoes ribosylation & phosphorylation intracellularly to become active as favipiravir-RTP.

It selectively & potently inhibits the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2, which prevents the viral transcription and replication.

When favipiravir-RTP is incorporated into a nascent RNA strand, it prevents RNA strand elongation and viral proliferation as well.



Mechanism of Action of Favipiravir

Clinical Studies

In one of Indian study on 150 patients, Favipiravir has shown clinical improvement of up to 88% in mild to moderate COVID-19 cases. It offers rapid reduction in viral load within 4 days and provides faster symptomatic and radiological improvement.

Currently, at least 18 clinical trials for COVID-19 involving more than 3,000 patients are ongoing across all countries and results from these studies have shown a positive outcome.

1.Favipiravir was associated with greater clinical recovery rate at 7 days (61% versus 52%) when compared with Umifenovir.

2.Favipiravir was associated with decreased median time to viral clearance (4days versus 11 days) and higher improvement rate on chest CT imaging on day 14 (91% versus 62%) compared with the control group receiving lopinavir/ritonavir (n=45); both groups also received aerosolized interferon α-1b.

3.In a retrospective, observational, multicenter study in 63 adults with COVID-19 in Thailand who received favipiravir (median loading dose of 47.4 mg/kg on day 1 and median maintenance doses of 17.9 mg/kg per day for a median total duration of 12 days), clinical improvement at day 7 was reported in 66.7% of patients and clinical improvement at day 14 was reported in 85.7% of patients.

4.In a prospective, randomized, multicenter study, favipiravir (n=120) was compared with umifenovir (n=120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% umifenovir).

Conclusion:
Favipiravir is expected to be an important therapeutic agent for severe influenza, the next pandemic influenza strain, and other severe RNA virus infections including SARS Cov-2 , for which standard treatments are not available.

Source: Shiraki k et.al; Pharmacol Ther. 2020 May; 209: 107512. Eric A comes et.al;Journal of Antimicrobial Chemotherapy, Volume 75, Issue 7, July 2020.

FOR MORE INFORMATION
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