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Medical Bulletin

Blue Cross Division

FAVIPIRAVIR (FAVIBLU): POTENTIAL ANTIVRAL FOR COVID-19

INTRODUCTION

The world has been battling the COVID-19 pandemic, which has affected almost every country for over 6 months now causing an enormous health as well as an economic burden. India has recorded more than 75 lakh cases with more than 110 thousand deaths causing a serious cause for concern. Easing lockdowns and reviving the economy is like a double-edged sword, with an increased risk of transmission of the disease.

One of the answers to this dilemma is a drug which can effectively control the infection at mild to moderate stage…FAVIPIRAVIR.

FAVIPIRAVIR

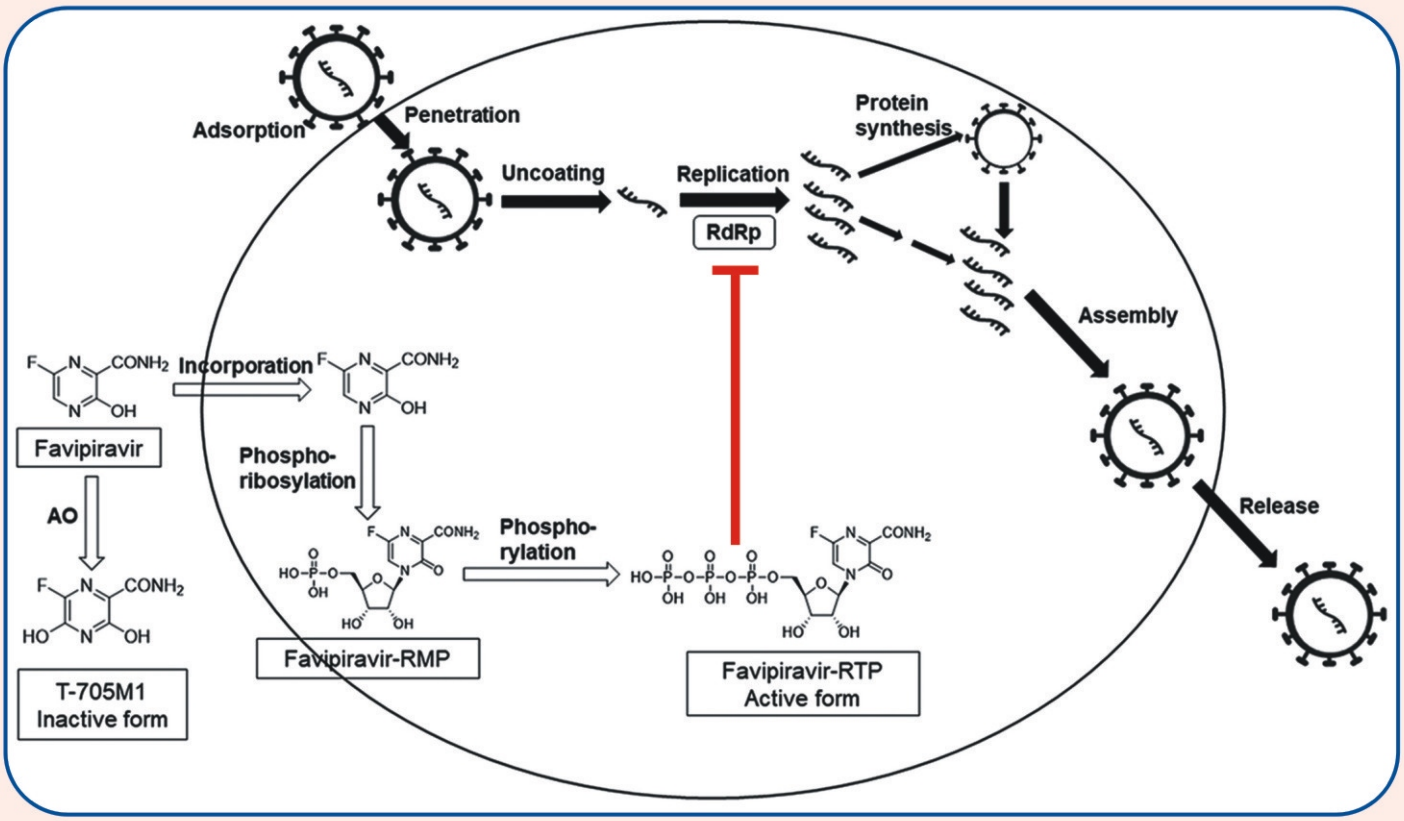
Favipiravir is a broad spectrum anti-viral agent, approved in Japan for treatment of influenza virus. It selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses, which is a crucial enzyme in the life cycle of SARS-CoV-2, thus halts the replication of the virus.

MODE OF ACTION

Favipiravir is a prodrug that is ribosylated and phosphorylated intracellularly to form its active metabolite Favipiravir ribofuranosyl -5′-triphosphate (T-705-RTP) or Favipiravir-RTP.

This competes with purine nucleosides and interferes with viral replication by incorporation into the virus RNA and potentially inhibits the RNA dependent RNA polymerase (RdRp) of RNA viruses, thus preventing 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.



Favipiravir: Mechanism of action

CLINICAL DATA

1. In a study conducted by the Ministry of Health of the Russian Federation, on 60 patients with COVID-19, where 40 patients received Favipiravir whereas 20 were on standard treatment, it was observed that the temperature of 68% of the patients returned to normal by the 3rd day as compared to the control group which was the 6th day. The complete elimination of the virus in patients taking Favipiravir took on an average 4 days as compared to the control group which took an average of 9 days.

According to the results, Favipiravir demonstrated safety with no new or previously unreported side effects detected and drug's efficacy was above a threshold of 80%, which is the criterion for a drug with high antiviral activity.

(https://www.thepharmaletter.com/article/latest-data-show-above-80-efficacy-for-favipiravir-in-covid-19-say-rdif-and-chemrar)

2. A study examined the effects of Favipiravir versus Lopinavir /Ritonavir for the treatment of COVID-19 where it was observed that the patients treated with Favipiravir showed a shorter viral clearance and a significant improvement in chest imaging [91.43% versus 62.22% (P = 0.004)] as compared to the control arm (Lopinavir/Ritonavir).
Patients treated with Favipiravir also presented with fewer adverse events as compared to the control arm showing a better therapeutic response on COVID-19 in terms of disease progression and viral clearance.
(https://www.sciencedirect.com/science/article/pii/S2095809920300631)

3. In an open-labeled, randomized, multi-centre trial to assess the safety and efficacy of Favipiravir on a total of 150 patients across India, a 28.6% faster total viral clearance was observed versus the control group, and on key secondary outcomes for clinical improvements, a 40% faster 'clinical cure' which was defined as normalization of clinical signs was demonstrated. It was also well tolerated without any serious adverse events.
(https://www.clinicaltrialsarena.com/glenmark-trial data)

4. In a randomized controlled study with sample size of hundred confirmed cases of covid, Favipiravir was compared with HCQ and Oseltamivir in Covid management.The average onset of SARS CoV 2 PCR negativity was 8.1 and 8.3 days in HCQ and Favipiravir arms respectively. This study concluded with Favipiravir as safe and effective alternative in mild to moderate covid 19 patients especially for those who are home quarantined where safety of HCQ is still questionable.
(https://www.researchsquare.com/article/rs-83677/v1)

CONCLUSION

Favipiravir is an antiviral drug that has a generally positive outlook all across the world, thanks to its effectiveness against the RNA-based influenza virus and hence The Drug Controller General of India has approved the use of Favipiravir (200 /400 mg Tablets) for the treatment of mild to moderate cases of COVID-19 in India.

Favipiravir has shown that early treatment with Favipiravir may improve clinical outcomes for mild to moderate patients and could potentially prevent patients from progressing to ARDS (Acute Respiratory Distress Syndrome) and mortality.

Source:
Furuta Y et al. Proc Jpn Acad Ser B Phys Biol Sci 2017; 93(7): 449-463; Vora A & Tiwaskar M. JAPI 2020; 68.

MEFENAMIC ACID (MEFTAL) IN THE MANAGEMENT OF COVID-19

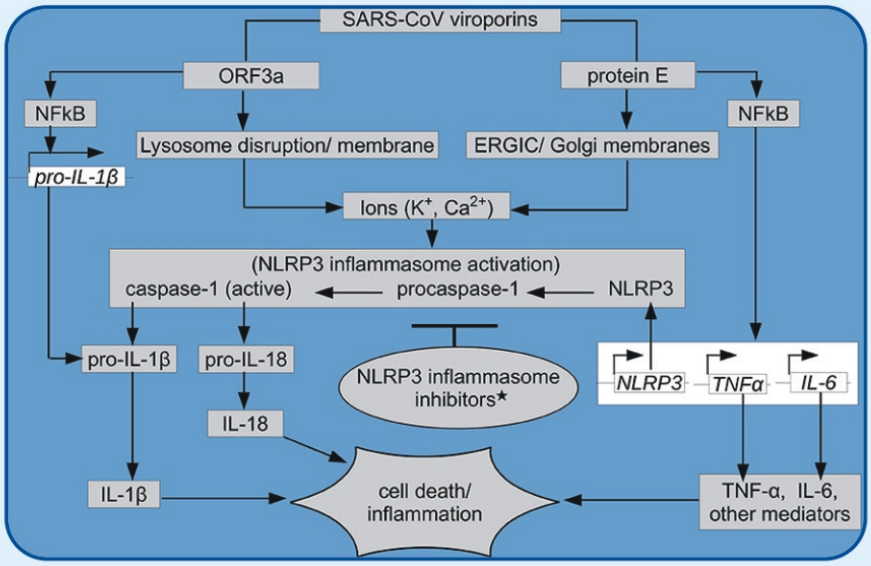
INTRODUCTION

SARS CoV-2 has caused a global pandemic with researchers all over struggling to find effective measures either to treat the virus or provide a supportive treatment for the patients and treat the symptoms.

The biggest threat to patients infected with the novel coronavirus is the severity of the body's immune response resulting in a cytokine storm making the disease worse. Hence, supportive treatment is one of the most important part in the management of patients suffering from the novel coronavirus worldwide.

Over time it has been learnt that one of the most common symptoms of SARS CoV-2 is presentation of fever, and hence most patients require an anti-pyretic to control the fever.

Paracetamol is commonly used for the treatment of the same, however, in certain cases it remains unresponsive and NSAIDs with established antipyretic action are being used.



Schematic representation of SARS-CoV viroporin-mediated NLRP3 inflammasome activation

Mefenamic Acid is one such anti-pyretic that is often use since last many decades. Literature evidence has shown that Mefenamic acid has anti-inflammatory, analgesic and antiviral actions and that may be of considerable value in the present coronavirus pandemic.

ANTI-PYRETIC

Mefenamic acid is a powerful inhibitor of the enzyme, Cyclooxygenase (COX), with a central and peripheral action. Due to this it is known to be a potent and powerful anti-pyretic and was found to be more effective and equally tolerable than Paracetamol in its antipyretic action in febrile illnesses.

ANTI-INFLAMMATORY ACTION OF MEFENAMIC ACID

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of anti-inflammatory drugs, inhibiting cyclooxygenase (COX) enzymes in the synthesis of prostaglandins and other mediators, and widely used for the treatment of pain and inflammation.

NLRP3 INFLAMMASOME

The NLRP3 inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of pro-inflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular damage.

MECHANISM OF RELEASE OF PRO-INFLAMMATORY CYTOKINES

It has been shown that several external and internal stimuli including viral RNA, activate the NLRP3 inflammasome via mechanisms such as formation of pores with ion-redistribution and lysosomal disruption, resulting in inflammation and associated cell death called pyroptosis.

Upon activation of the NLRP3, its procaspase-1 is converted into the active effector protease caspase-1, which then causes cleavage and maturation of pro- inflammatory cytokines such as pro-interleukin 1β (pro-IL- 1β) into its active form IL-1β as well as that of IL-18. These trigger a cascade of other downstream mediators of inflammation such as interleukin 6 (IL-6), tumour necrosis factor (TNF), prostaglandins and leukotrienes.

ROLE OF NLRP3 IN SARS CoV-2

Infection with SARS-CoV-2 is known to induce a storm of pro-inflammatory cytokines, especially IL-1β, IL-6, and TNF-α, which play an important role in the progression of tissue inflammation causing acute respiratory distress syndrome ARDS, which is a form of acute lung injury (ALI) and often leads to death.

Although, innate immune mechanisms such as optimal activation of the NLRP3 inflammasome plays an important role in antiviral host defences, its aberrant activation and downstream mediators often lead to pathological tissue injury.

MEFENAMIC ACID AND NLRP3 INFLAMMASOME

Studies have shown that, unlike other NSAIDs, only fenamates like mefenamic acid selectively inhibit the NLRP3 inflammasome and IL-1β release via inhibiting the membrane volume regulated anion (Cl^-) channel (VRAC), independent of its cyclooxygenase-1 (COX-1) mediated anti-inflammatory activity.

Some studies have also pointed a role of mefenamic acid in exhibiting anti-viral properties along with its anti-pyretic and anti-inflammatory actions where it has shown to have a high inhibitory effect against RNA viruses which may be attributed to its ability to inhibit the viral protease enzyme activity.

CONCLUSION

In agreement with these findings, mefenamic acid has shown to exhibit a strong anti-inflammatory action in SARS CoV-2 infection characterized by a cytokine storm by blocking the NLRP3 inflammasome that causes the release of pro-inflammatory cytokines.

Hence, apart from its established anti-pyretic action, mefenamic acid can be an important therapeutic component in management of viral infections, especially SARS CoV-2.

Source:
Pareek RP. International Journal of Science and Research 2020; 9(6): 1-6; Shah A. Frontiers in Immunology 2020; 11(1021): 1-5; Cemolai N. Expert Rev Clin Pharmacol 2013; 6(3): 289-305.

VITAMIN D (BLUVIT-D3) AND COVID-19

Over the years, randomized controlled trials have revealed the protective effects of vitamin D against acute respiratory infections. Given the current pandemic caused by the SARS CoV-2 virus, a striking overlap between risk factors for severe COVID-19 and vitamin D deficiency, including obesity, older age, and ethnic origin, has led some researchers to hypothesize that vitamin D supplementation could hold a promise as a preventive or therapeutic agent for COVID-19. Vitamin D metabolites have long been known to support innate antiviral effector mechanisms, including induction of antimicrobial peptides and autophagy.

With the current pandemic, lower circulating 25(OH)D concentrations have been reported to be associated with an increased susceptibility to SARS-CoV-2 infection and with COVID-19 severity.

From a mechanistic angle, it can be postulated that vitamin D favourably modulates host responses to SARS-CoV-2, both in the **early viraemic phase** and later in **hyper inflammatory phases** of COVID-19.

ROLE OF VITAMIN D IN EARLY VIRAEMIC PHASE

ANGIOTENSIN CONVERTING ENZYME-2 (ACE-2) AND SARS CoV-2

The SARS-CoV-2 virus enters into human cells via the ACE-2 receptor. During the course of infection, the virus particles bind to ACE-2 and get internalized into human cells. Moreover, SARS-CoV 2 virus was shown to downregulate the ACE-2 protein expression.

This would imply that the loss of ACE-2 function may develop during SARS CoV-2 infection and since ACE-2 receptor is a key player in RAS, its loss of function can lead to serious consequences. The loss of ACE-2 function can be a prime event that leads to increased neutrophil infiltration in the lung and results in exaggerated inflammation and injury. As soon as the ongoing lung infection results in hypoxia, the stakes are further raised by induction of renin release and increase in renin gene expression that can lead to a vicious circle.

ROLE OF VITAMIN D

Mounting evidence indicates that vitamin D is a negative endocrine regulator of RAS, and that normalization of vitamin D levels can lower RAS activity via transcriptional suppression of renin expression and the ACE/Ang II/AT1R cascade.

Also, the active form of Vitamin D, calcitriol, has shown to exhibit protective effects against acute lung injury by modulating the expression of members of RAS which are the ACE-2 receptors in the lung tissue, supporting the role of vitamin D deficiency as a pathogenic factor in COVID-19.

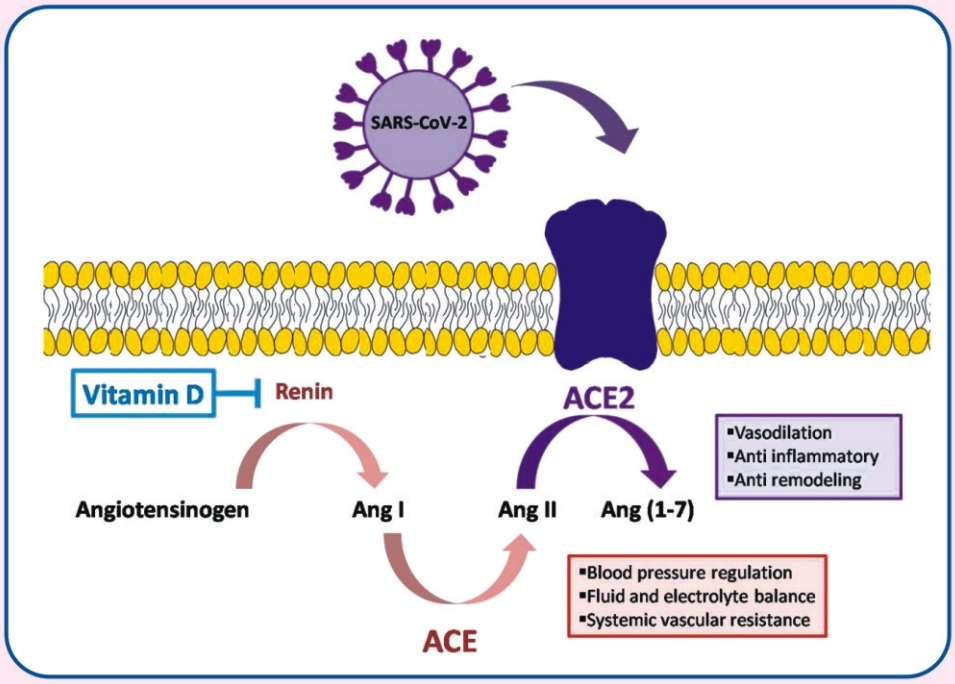
ROLE OF VITAMIN D IN HYPERINFLAMMATORY PHASE

CYTOKINE STORM IN COVID-19

Cytokine storm is an acute hyper inflammatory response that may be responsible for critical illness in patients infected with SARS CoV-2.

As a response to the SARS-CoV-2 infection, macrophages and dendritic cells trigger an initial immune response, including lymphocytosis and cytokine release.

However, in some cases, the inflammatory response results in the destruction of lymphocytes attempting to stop SARS-CoV-2 infection. Lymphopenia ensues, especially in patients severely affected and the cascade of cytokine storm ensues which begins with the disruption of the epithelial barrier in the lungs exposing the lungs and other tissues to infection. The cytokine production becomes rapidly dysregulated, resulting in the damage of healthy cells typically first in the lungs but potentially spreading to other organs including the kidneys, heart, blood vessels, and brain.



ACE2 , RAS and Vitamin D

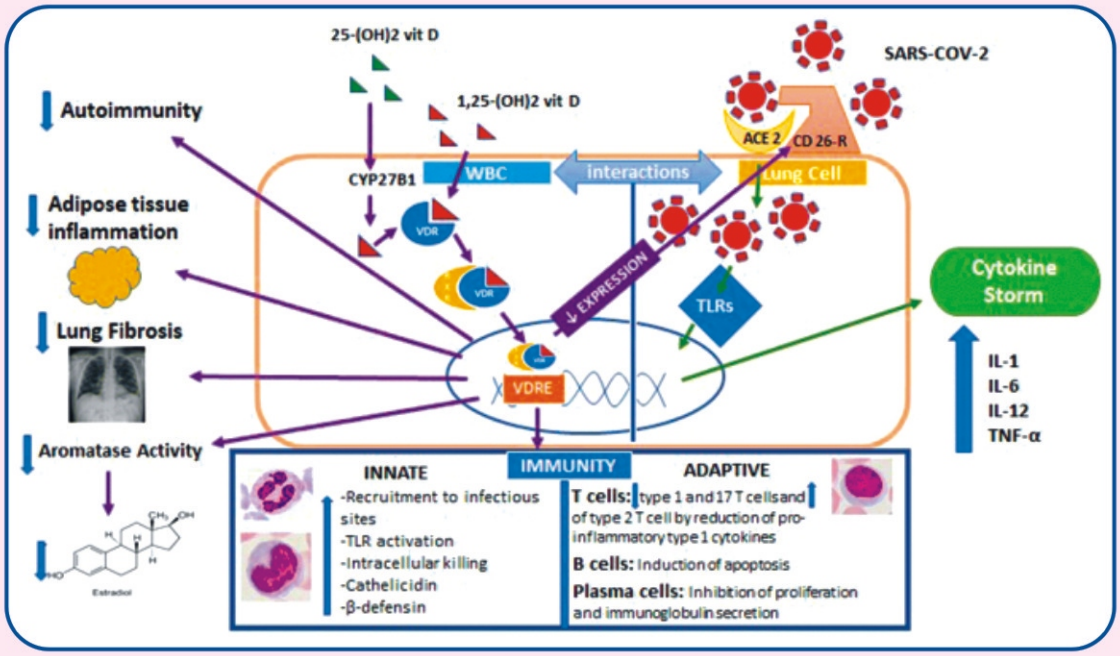
ROLE OF VITAMIN D

The innate immune system generates both pro-inflammatory and anti-inflammatory cytokines in patients suffering from COVID-19. Multiple studies have demonstrated the role of vitamin D in regulating the immune system.

Calcitriol (1,25-dihydroxy-cholecalciferol) acts as an immune system modulator by down-regulating the expression of pro-inflammatory cytokines and enhancing macrophage function. Furthermore, it induces the expression of potent antimicrobial peptides (AMPs), which are present in natural killer cells, monocytes, neutrophils, as well as the epithelial cells lining the respiratory tract.

Vitamin D triggers development of suppressive regulatory T cells and inhibits development of pro-inflammatory Th17 cells.

Vitamin D may suppress cytokine production by simultaneously boosting the innate immune system and reducing the over activation of the adaptive immune system in response to increased viral load.



Principal functions of vitamin D

Hence, the pro-inflammatory peptides of the adaptive immune system are modulated by vitamin D, particularly those involved in acute inflammation cytokine storms.

CONCLUSION

Dearth of treatment for COVID-19 leaves us with no choice but to take precautionary and prophylactic measures to stand a better chance to fight this pandemic. It has been shown that a correlation exists between vitamin D levels and COVID-19 susceptibility and that vitamin D could prove to be an essential element in our fight against COVID-19.

Hence, maintaining adequate vitamin D levels is vital to prevent getting infected or to ward off the infection without mortality, in case it occurs.

Source:
Martineau AR & Forouhi NG et al. The Lancet: Diabetes & Endocrinology 2020; 8(9): P735-P7336. Garami AR et al. BMJ 2020; 368;Suvarna VR & Mohan M. J of Diabetology 2020; 11(2): 71-80. Bhaskar S et al. Frontiers in Immunology 2020;Razdan K et al. Med Drug Discov 2020; 7: 100051. Ghavideldarestani M et al. https://www.preprints.org/manuscript/202004.0355/v;Daneshkhah A et al. Aging Clin Exp Res 2020; 2 : 1-18.

For More Information: **Dr. Prabhu Kasture** (MD, DPH), GM- Medical Services. **Call:** 022 66638043 **e-mail:** prabhu.k@bluecrosslabs.com **Correspond:** Blue Cross Laboratories Pvt Ltd. Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013

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