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Drug's repurposing for Covid-19: A comprehensive Review

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ABSTRACT:
The global pandemic caused by the 2019 coronavirus illness (COVID19), which first appeared in Wuhan, China, in December 2019, has put the public's health at risk. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which is the cause of COVID19, has been linked to more than 4 million cases as of May 11, 2020. The primary ways that SARS-CoV2 spreads are through respiratory droplets and close contact. It is a highly virulent and transmissible coronavirus. A rising collection of clinical evidence indicates that a cytokine storm is both a significant factor in COVID-19 fatality and is associated with COVID-19 severity. There is an urgent need to comprehend the cytokine storm in COVID19 given the lack of antiviral and vaccines for the disease. 4 million cases of COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been confirmed as of 11 May 2020. SARS-CoV-2 is a highly pathogenic and transmissible coronavirus that primarily spreads through respiratory droplets and close contact. A growing body of clinical data suggests that a cytokine storm is associated with COVID-19 severity and is also a crucial cause of death from COVID-19. In the absence of antiviral and vaccines for COVID-19, there is an urgent need to understand the cytokine storm in COVID-19. Here, we have reviewed the current understanding of the features of SARS-CoV-2 and the pathophysiological mechanisms, and treatments of various drugs which are repurpose in COVID-19. They all are act by different mechanism to stop the spread of covid-19

Keyword: Covid-19, Repurposing, Pandemic, cytokine storm, Inflammation.

I. INTRODUCTION:

The expression of proinflammatory genes, especially chemokines, was markedly elevated in COVID-19 cases compared to community-acquired pneumonia patients and healthy controls, suggesting that SARS-CoV-2 infection causes hypercytokinemia. Compared to SARS-CoV, which is thought to induce inadequate interferon (IFN) responses, SARS-CoV-2 robustly triggered expression of numerous IFN-stimulated genes (ISGs). These ISGs exhibit immunopathogenic potential, with over representation of genes involved in inflammation. The transcriptome data was also used to estimate immune cell populations, revealing increases in activated dendritic cells and neutrophils. The COVID-19 outbreak caused by SARS-CoV-2 infection has been declared as a global pandemic. Typical clinical symptoms of COVID-19 are fever, cough, myalgia, and short-ness of breath. Severe cases often develop acute lung injury, or the fatal form, acute respiratory distress syndrome (ARDS) . To date, no specific antiviral treat-ment is available for COVID-19 [1].Although the COVID-19 vaccine programme continues to be rolled out globally, there is still a need to identify effective treatments, particularly in countries where vaccine uptake is slow, and with the insidious threat of mutations resulting in vaccine escape. With the urgency of the pandemic making the timely discovery of new drugs almost impossible, the idea of repurposing existing drugs to treat COVID-19 is an attractive strategy, especially if they are already approved (for other indications) and have well established safety profiles. Hundreds of medications have been trialled in mainly hospitalised patients with COVID-19, creating a huge amount of data of differing qualities The project, discussed by CSTL director David Fajgenbaum, has done randomized trial on 340000 patients. As Fajgenbaum describes in the podcast, "out of those over 400 drugs that have been tried, just a few of them have been definitively shown to be effective". The database has ranked only four drugs with a grade A: baricitinib, remdesivir, dexamethasone, and tocilizumab[2]. Guidance issued globally follows these data to some degree. For example, US guidelines recommend. the use of dexamethasone in hospitalised patients who require supplemental oxygen or mechanical ventilation, and state that the addition of tocilizumab to dexamethasone improves survival. They also recommend the use of

International Journal of Pharmaceutical Research and Applications
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remdesivir in hospitalised patients with COVID-19 who require supplemental oxygen but not those who require mechanical ventilation. UK guidelines recommend offering dexamethasone to patients who need supplemental oxygen; or tocilizumab to those who need supplemental oxygen. They make conditional recommendations to consider remdesivir for adults with COVID-19 pneumonia on supplemental oxygen but not those on mechanical ventilation. The clinical trial data are also important for ruling out drugs that have not been effective for COVID-19. Platform trials, such as RECOVERY and SOLIDARITY, testing multiple drugs showed that hydroxychloroquine, lopinavir– ritonavir, and interferon did not reduce mortality. Also, on the basis of trial data, the European Medicines Agency, the US National Institutes of Health, and WHO have advised against using ivermectin outside clinical trials, since higher than approved doses would be needed for efficacy against the virus, which increases the risk of side effects[3]. Favipiravir is also have been approved by Indian Drug Regulator for the treatment of covid-19 in India.

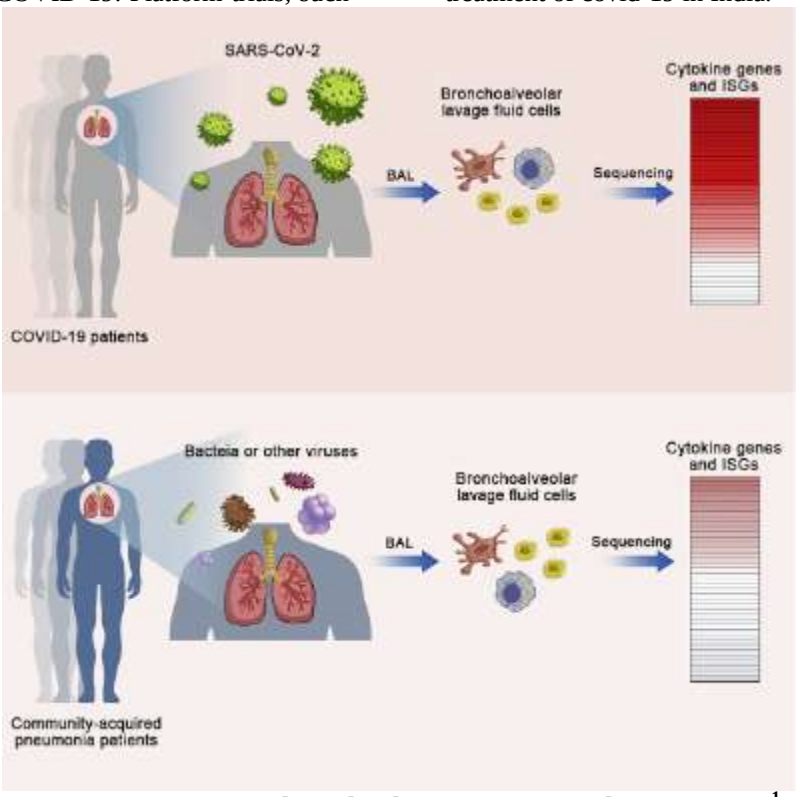

Fig1: Comparative cytokinin level in pneumonia and SARS-Cov-2 [1]

1)Favipiravir:

Favipiravir is one such oral drug that was approved for new and reemerging pandemic influenza in Japan in 2014 and has shown potent in vitro activity against severe acute respiratory syndrome coronavirus-2.Recently, in the month of June 2019, it has been approved in India by the Indian Drug Regulator under accelerated approval process for the treatment of mild to moderate COVID-19 under restricted emergency use. From the clinical studies in COVID-19, it has shown rapid viral clearance as compared to lopinavir/ritonavir (LPV/RTV) and superior recovery rate than umifenovir [4]

MECHANISM

Favipiravir (prodrug) is a purine base analog that is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation. It is a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNAviruses. Favipiravir is incorporated into the nascent viral RNA by error prone viral RdRp, which leads to chain termination and viral mutagenesis. The RdRp existing in various types of RNA viruses enables a broader spectrum of antiviral activities of favipiravir After RNA viral incorporation, favipiravir-RTP works as a mutagen, which is capable of fleeing coronavirus repair machinery. The favipiravir-RTP adds to the

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pressure on CoV nucleotide content, which already has a low cytosine (17.6%)in the SARS-CoV-2 genome. In total, along with the increased frequency of mutation,favipiravir-RTP has a positive effect on SARS-CoV-2 by a cytopathic effect, which is induced by the virus, reduction in the number of viral RNA, and infectious particles[5].

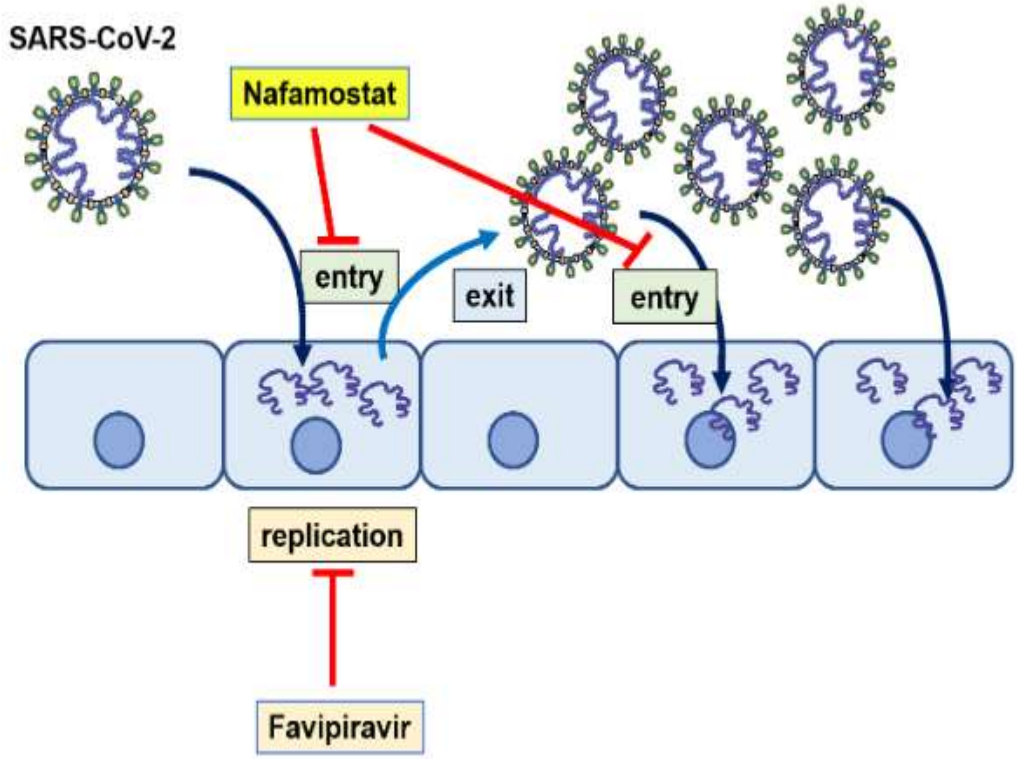

Fig2:.Mechanism of action of Favipiravir [6]

2) Tocilizumab

Previously tocilizumab was used for idiopathic arthritis, rheumatoid arthritis, and giant cell arteritis. Tocilizumab, which is the IL-6 receptor antagonist, Recently has been approved by the US FDA for the treatment of cytokine release syndrome (CRS), is expected to treat cytokine storm caused by COVID-19[7]

MECHANISM

The mechanism of tocilizumab in the treatment of COVID-19 remains unclear. According to previous studies, IL-6 is secreted by almost all stromal cells and immune system cells, such as B lymphocytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells and other non-lymphocytes, such as fibroblasts, endothelial cells, keratinocytes, glomerular mesangial cells and tumor cells[8] . Under normal circumstances, the level of IL-6 in the body is very low, and it can be quickly synthesized to strengthen the body's defense function when there is an infection or injury. Excessive release of IL-6 can cause CRS, and the more severe the CRS, the higher the serum peak concentration of IL-6. IL-6 binds to its receptor IL-6R to form a complex, and then binds to the signal transducer glycoprotein 130 (gp-130) to initiate signal transduction and trigger downstream signal transduction and gene expression. IL-6R exists not only in membrane-bound form (mIL-6R), but also in soluble form (sIL-6R). In the classical signal transduction pathway, IL-6 binds to mIL-6R to form a complex, and then binds to gp-130, causing downstream reactions, such as anti-infammatory efects[9], that are limited to such cells that express mIL-6R. In the trans-signaling pathway, IL-6 forms a complex with sIL-6R and gp-130, which initiates intracellular signal transduction in the absence of mIL-6R, and the pathway has infammatory efects . The next steps were to induce the synthesis of acute reactive protein through two completely diferent signaling pathways. One IL-6 signaling pathway is mediated by the JAK/STAT tyrosine kinase system, while the other is mediated by the Ras/mitogenactivated protein kinase (MAPK)/NF-

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κB-IL-6 pathway. The former is a major pathway . In the classical signal pathway, many cells cannot respond to IL-6 signal because of the lack of expression of IL-6R, while some of these cells can be stimulated by sIL-6R-IL-6 complex to respond to IL-6 signal and cause cell signal transduction . The trans-presentation signal is suppressed by extracellular gp-130, and extracellular gp-130 can form a complex with sIL-6R to prevent sIL-6R from binding to membrane-bound gp-130 . The classical signal is limited to the cells (macrophages, neutrophils, T cells, etc.) that express IL-6R, and plays a leading role in the low level of IL-6. However, when the level of IL-6 increases, IL-6 signal is widely expressed, because gp-130 is everywhere. In this way, IL-6 trans signaling via the sIL-6R can activate virtually all cells of the body and then regulate pro-infammatory reactions. Blocking of trans-signaling was efective in a variety of preclinical chronic and autoimmune disease models . Tocilizumab, which is a humanized anti-IL-6R monoclonal antibody, can bind to both mIL-6R and sIL-6R and then inhibit classical and trans-signals. This may be its potential mechanism for the treatment of cytokine storm in COVID19 [10,11]

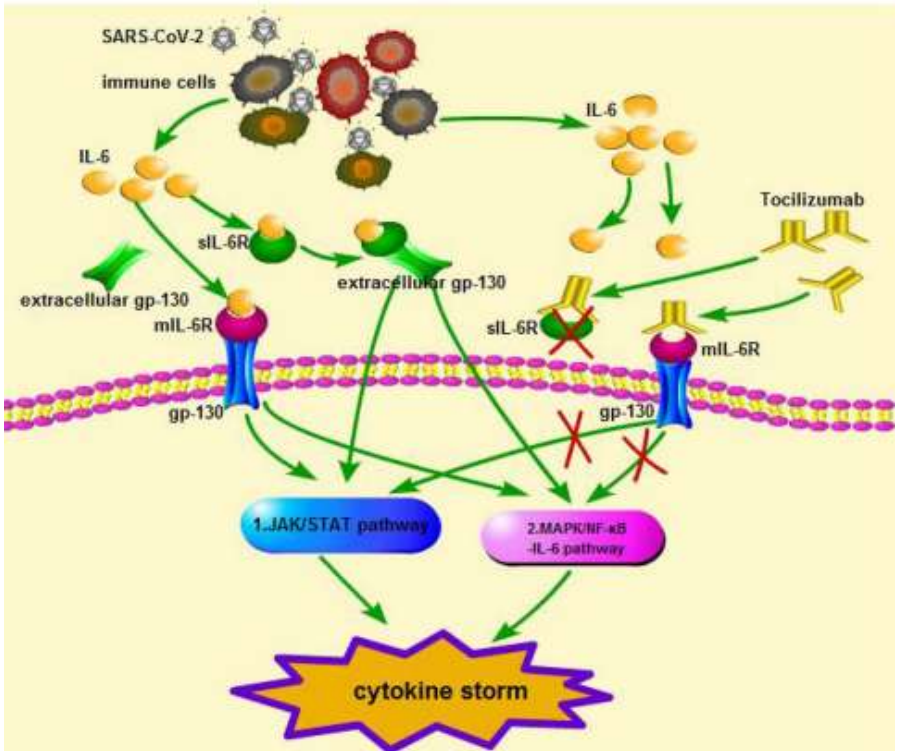

Fig. 3: The potential mechanism of tocilizumab in the treatment of cytokine storm[7]

3)Ivermectin

Ivermectin is an FDA-approved broad spectrum anti-parasitic agent. Along with other groups drugs,have shown to have anti-viral activity against a broad range of viruses in vitro. Originally identified as an inhibitor of interaction between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the import in (IMP) , Ivermectin inhibit IN nuclear import and HIV-1 replication. Other actions of ivermectin are ivermectin has been shown to inhibit , including simian virus SV40 large tumour antigen (T-ag) and dengue virus (DENV) .RNA viruses such as DENV , West Nile Virus , Venezuelan equine encephalitis virus (VEEV) and influenza. Effective against the DNA virus pseudorabies virus (PRV) both in vitro and in vivo.Ivermectin was in phase III clinical trial in Thailand Since 2014, against DENV infection, in which a single daily oral dose was observed to be safe[12].

MECHANISM

In the treatment of COVID19The causative agent of the current COVID-19 pandemic, SARS-CoV-2, is a single stranded positive sense RNA virus that is related to severe acute respiratory syndrome coronavirus (SARS-CoV). Studies on SARS-CoV proteins have revealed a potential role for IMPα/β1 during infection in signal-dependent nucleocytoplasmic

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1205-1215 www.ijprajournal.com ISSN: 2456-4494

shutting of the SARS-CoV Nucleocapsid protein, that may impact host cell division. In addition, the SARS-CoV accessory protein ORF6(produce polyprotein which involed in viral replication) is antagonize by ivermectin by sequestering IMPα/β1 on the rough ER/Golgi membrane.Taken together, these reports suggested that ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2 [13].

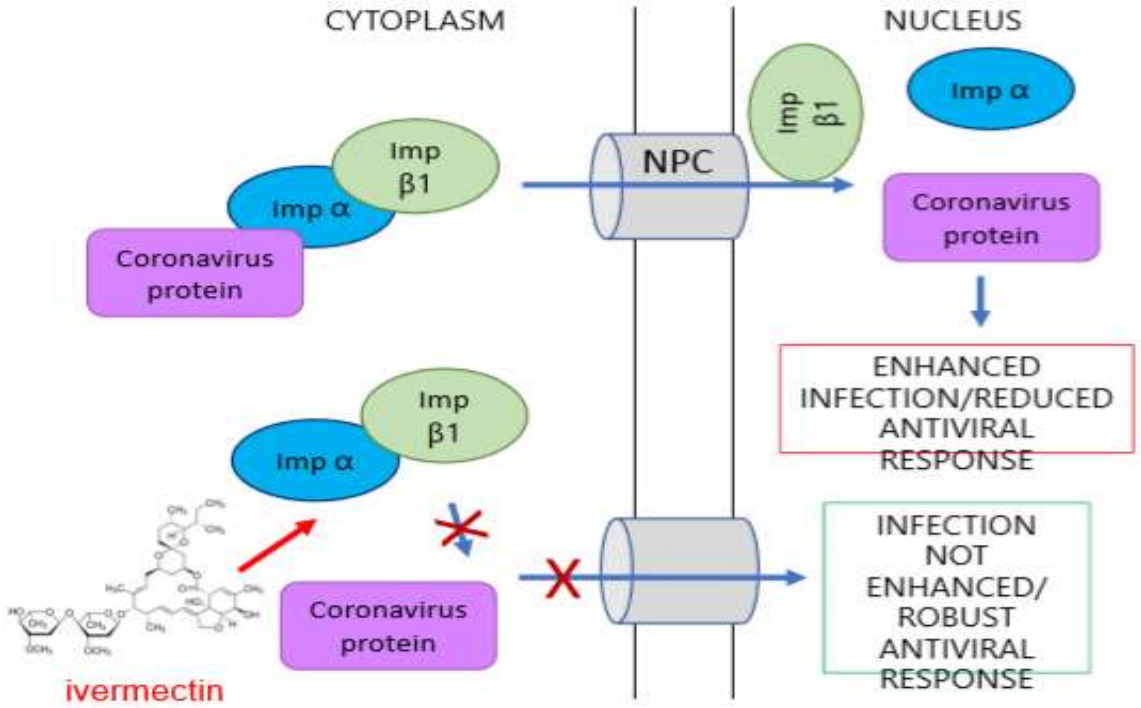

Fig:4. The potential mechanism of IVERMECTIN in the treatment of covid-19[13]

4) Steroids

Corticosteroid is used to treat patients with-Severe human coronavirus infections,Severe acute respiratory syndrome (SARS),Middle East respiratory syndrome-related coronavirus(MERS), and Other severe respiratory virus infections.In accordance with current WHO guidance, Russell and colleagues recommend that corticosteroids should not be used in 2019-nCoV-induced lung injury or shock, except in the setting of a clinical trial. Moreover, there are studies supporting the use of corticosteroids at low-to-moderate dose in patients with coronavirus infection.E.g Dexamethasone is a corticosteroid used in a wide range of conditions for its anti-inflammatory and immunosuppressant effects[14]. Systematic reviews of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids[15].Methylprednisolone has already been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy[16]Studies indicate that short-term moderate-dose corticosteroid plus immunoglobulin is effective for reversing the continued deterioration of COVID-19 patients who failed to respond to the low-dose therapy.[17].

MECHANISM

Corticosteroids do not directly inhibit virus replication, their main role is anti-inflammatory and suppress immune response.The main anti-inflammatory effect of glucocorticoids is to inhibit a large number of pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors to address the inflammatory process and restore homeostasis. In the early stage of

International Journal of Pharmaceutical Research and Applications
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inflammation, glucocorticoids reduce capillary dilation, inflammatory cell exudation, leukocyte infiltration, and phagocytosis.In the late stage, glucocorticoids can inhibit the excessive proliferation of capillaries and fibroblasts.These explained why corticosteroids therapy was more needed in severely ill patients with coronavirus infection[18].

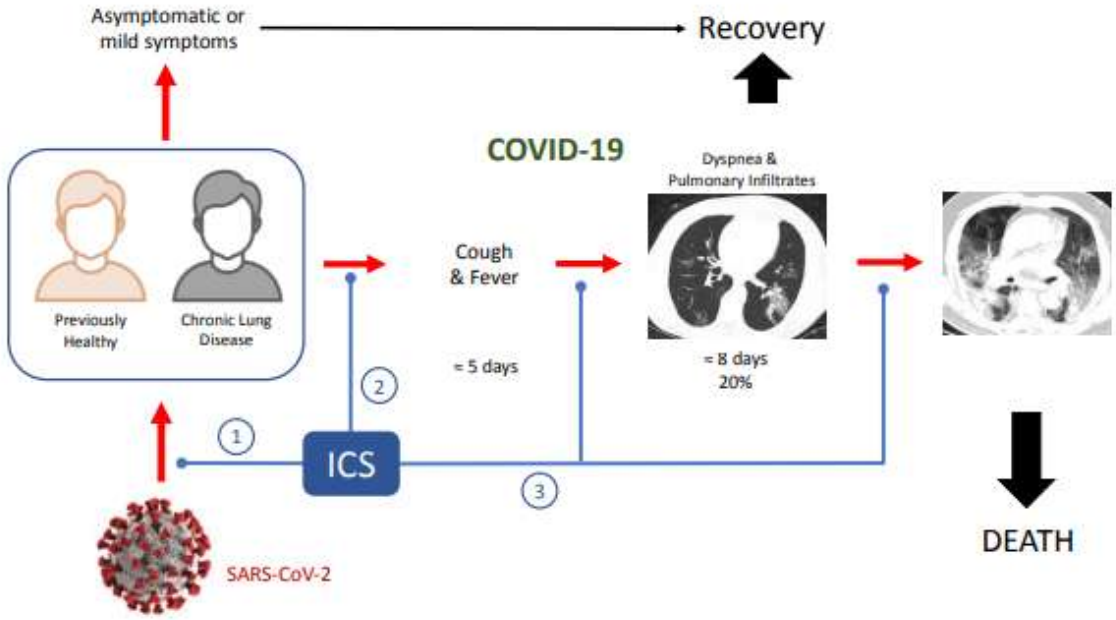

Fig.:5 The potential mechanism of Corticosteroid in the treatment of covid-19[19]

5] Hydroxychloroquine

Antimalarial drugs such as chloroquine and hydroxychloroquine have been in the market for over a century. These drugs have been used not only for malaria but also for several rheumatic diseases given their anti-inflammatory properties, affordability and the fact that they have shown a good safety profile. Knowing that these drugs have proven effective for a wide range of diseases has made several researchers wonder about their use in other areas such as cancer and viral infections. This is why, in the midst of a global pandemic, the question of antimalarial use in treatment and prophylaxis of covid-19 has been raised.[20]

MECHANISM

The effect of hydroxychloroquine and chloroquine on viral replication goes beyond cytokine inhibition. These medications are weak bases that can affect acid vesicles and inhibit several enzymes. This characteristic allows them to inhibit the viral entry to the cell when the endocytosis is pH dependent. It also inhibits glycosyl-transferases, viral post-translational modifications and replication of some viral families. The antiretroviral effect has been considered to be caused by the inhibition of viral glycosylation, a major antiviral mechanism of these drugs. It was also recently described that chloroquine might inhibit quinone reductase-2, an enzyme involved in sialic acid biosynthesis. If this were to be true, it would explain further its effect on HIV, SARS and orthomyxoviruses because sialic acid is present on HIV1 glycoproteins, SARS angiotensin-converting enzyme 2 (ACE2 receptor and orthomyxovirus receptors)[20]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1205-1215 www.ijprajournal.com ISSN: 2456-4494

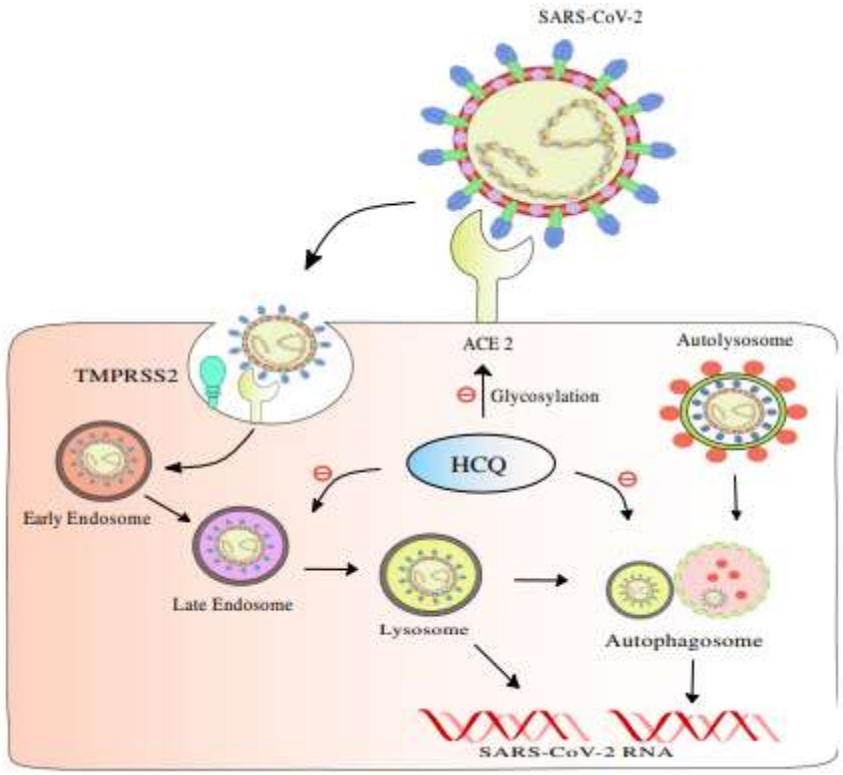

Fig:6 The potential mechanism of Hydroxychloroquine in the treatment of covid-19[21]

6) Baricitinib

Baricitinib, sold under the brand name Olumiant among others, is a medication used for the treatment of rheumatoid arthritis, alopecia areata, and COVID-19. It acts as an inhibitor of janus kinase (JAK), blocking the subtypes JAK1 and JAK2.Baricitinib is approved for medical use in the European Union and in the United States.An important side effect of JAK inhibitors is serious bacterial, mycobacterial, fungal and viral infections[22].

MECHANISM

Baricitinib not only interrupts the passage and intracellular assembly of SARS-CoV-2 into the target cells but it also reduces the inflammation in patients with ARDS. In severe COVID-19 cases, the JAKSTAT signaling pathway participates the cytokine storm. Excessive amounts of cytokines bind to their receptors and activates JAKs, which occurs upon ligand-mediated receptor multimerization, since two JAKs are close enough for trans-phosphorylation[24] . The activated JAKs phosphorylate the receptors, activate and phosphorylate their main substrate STATs. Phosphorylated STAT dimerizes with other members of STAT family with conserved SH2 domains. Finally, the dimerized STATs in the cytoplasm are transferred into the nucleus and combine to specific DNA elements to regulate the expression of cytokine-responsive genes. Subsequently, cytokine storm was finally induced. Baricitinib is an ATP competitive kinase inhibitor that inhibits selectively, effectively, and reversibly JAK1/JAK2. By suppressing JAK1/ JAK2, baricitinib intracellularly inhibits the proinflammatory signal of several cytokines, such as IL-6, IL-12, IL-23 and IFN-γ. It has been demonstrated clinical benefits for the patients with moderate or severe RA, including reducing the incidence of structural joint damage . This drug might to lower the hyper inflammation, or so-called cytokine storm caused by SARS-CoV-2, that would prevent damage to the lungs and possibly other organs . However, there are some different views on the theory of baricitinib to treat cytokine storms, which needs to be clarified. In certain pathological conditions, the inflammatory process is widely recognized as a localized protective response of the body when it is attacked by pathogens, such as SARS-CoV-2. The JAK-STAT is the primary signaling pathway regulated by cytokines and is

International Journal of Pharmaceutical Research and Applications
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crucial for initiating the innate immunity, orchestrating the adaptive immune mechanisms, and finally constraining the inflammatory and immune responses[25] . It seems that using a JAK1/JAK2 inhibitor to treat a viral disease might appear illogical given that the antiviral effects of IFN are largely mediated by the JAK-STAT signalling pathway. So, it is speculated here that in early asymptomatic disease and stages of the disease not requiring admittance to hospital, approximately 80% of COVID-19 patients are able to clear the virus through endogenous antiviral mechanisms, certainly including the IFN. Therefore, it is not recommended that baricitinib or other JAK inhibitors be given to these individuals[26] . However, both COVID-19 and SARS are characterized by an over exuberant inflammatory response, akin to a so-called cytokine storm, and viral load is not correlated with the worsening of symptoms[27] . The clinically severe phase of COVID-19 is accompanied by high levels of cytokine signalling, all of which signal through the JAK-STAT pathway. This finding suggests that when hospital care is required for patients with a pathogenic SARS-CoV-2 infection, JAK-STAT pathway inhibition might be a potential strategy. In patients with moderate disease requiring hospital care, the peak SARS-CoV-2 load occurs within approximately 7 days of symptom onset, and later, as the viral titre decreases in some patients, cytokine storm, causes the severe phase of the diseases[28].

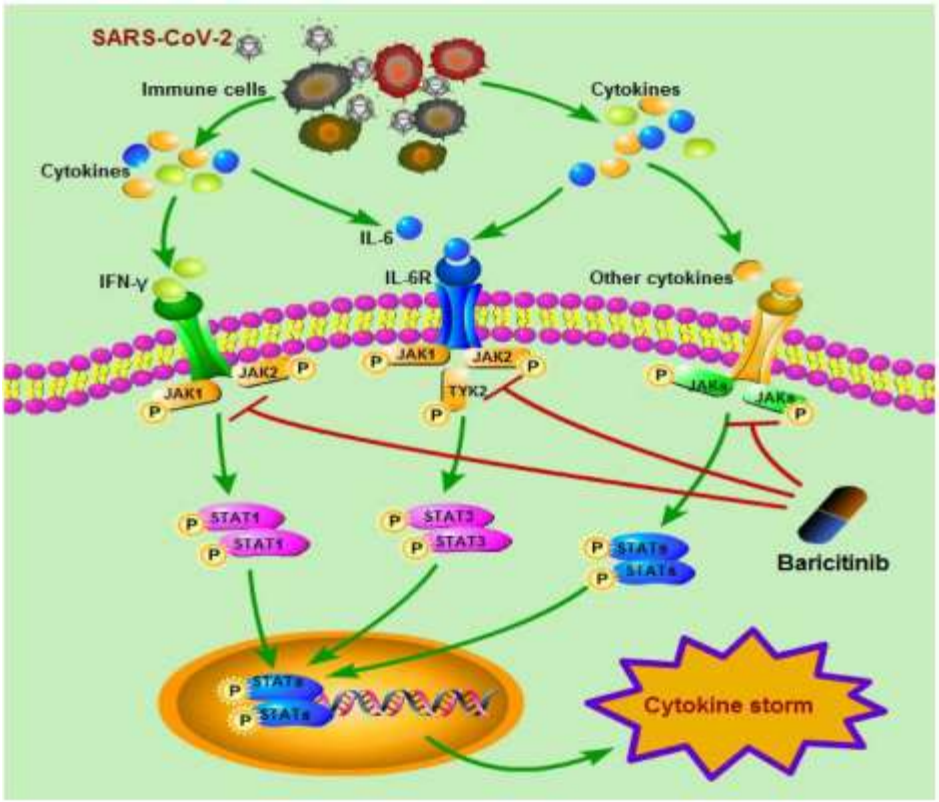

Fig.:7 The potential mechanism of Baricitinib in the treatment of covid-19[23]

7) Remdesivir

Remdesivir was originally developed to treat hepatitis C,and was subsequently investigated for Ebola virus disease and Marburg virus infections' In November 2020, the FDA issued an emergency use authorization (EUA) for the combination of baricitinib with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized people two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) he most common adverse effects in people treated with remdesivir were respiratory failure and blood biomarkers of organ impairment[29].

MECHANISM

Remdesivir's antiviral activity, sterically interacting with the viral RdRp to induce delayed chain termination, has been demonstrated in vitro

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against multiple coronaviruses (SARS, MERS, contemporary human CoV and bat-CoVs). Remdesivir was also shown to perturb pan-CoV RdRp function by inhibiting viral replication of SARS, MERS, and the model βcoronavirus murine hepatitis virus (MHV), even in settings with intact exonuclease proofreading activity.Biochemical data from recombinant respiratory syncytial virus (RSV) RdRp suggested the primary mechanism of action was through delayed chain termination. Importantly, remdesivir inhibits viral replication (demonstrated with both Ebola and RSV) in cell-based assays with IC50 values of approximately 100 nM, whereas human RNA Polymerase (RNAP) II and human mitochondrial RNAP are not inhibited in the presence of compound, providing approximately 500-fold selectivity. This selectivity is achieved, at least in part, due to the nucleoside analogues being poor substrates for the human polymerases. Interestingly, in vitro assays demonstrate that the triphosphate form of the inhibitor was incorporated at increased rates compared to natural nucleotide pools, likely adding to strong antiviral potency of remdesivir through premature RNA synthesis termination[30].

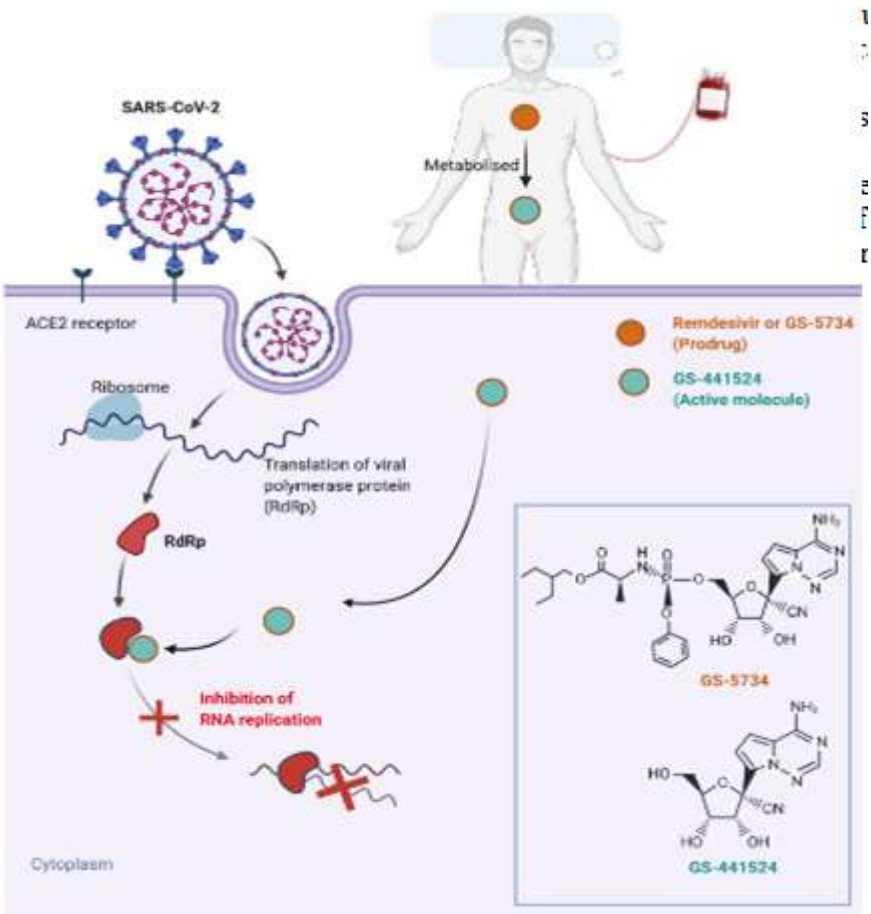

Fig.8 The potential mechanism of REMDESIVIR in the treatment of covid-19[30]

II. CONCLUSION

The effectiveness of drug repurposing strategies is determined by whether such agents will compare with virus-specific vaccines or small molecules. A broad-spectrum strategy may have fundamental flaws, much like antibiotics, as more virulent, drug-resistant strains emerge. Drugs like remdesivir and chloroquine have essentially suffered from fallacies against COVID-19 as preclinical assumptions overestimate their clinical efficacy. This shows that even repurposed drugs may require extensive clinical trials. However, a global health emergency of the magnitude of the COVID-19 pandemic calls for a bold medical intervention, where speed is of utmost importance. Drug repurposing cuts down a substantial amount

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1205-1215 www.ijprajournal.com ISSN: 2456-4494

of research time and the effective cost. Such strategies may also uncover the effectiveness of drugs that have otherwise failed to demonstrate their efficacy against the original target.Ivermectin is an inhibitor of the COVID-19 causative virus (SARS-CoV-2) in vitro. A single.Ivermectin is FDA-approved for parasitic infections, and therefore has a potential for repurposing. Ivermectin is widely available, due to its inclusion on the WHO model list of essential medicines. Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance, Methylprednisolone has already been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy. Favipiravir is one such oral drug that was approved for new and reemerging pandemic influenza in Japan in 2014 and has shown potent in vitro activity against severe acute respiratory syndrome coronavirus-2. Tocilizumab, which is the IL-6 receptor antagonist, Recently has been approved by the US FDA for the treatment of cytokine release syndrome (CRS), is expected to treat cytokine storm caused by COVID-19.

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