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Review Article

The Review on current treatments and therapies on COVID-19

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A B S T R A C T

Coronavirus are enveloped RNA Virus related to family 'Coronaviride'. In December 2019, many pneumonia cases reported by patients with unknown causes mainly associated with seafood and wet market in when China and they are clinically resembled with viral pneumonia at present time there is no antiviral drug for the treatment of COV infection but some drugs and therapies gives effective action in the treatment and prevention of the SAR-COV-1 and MERS COV and these particular drugs and therapies plays important role in prevention and cure of SARS-COV-2 (COVID-19) such as Hydroxy-chloroquine and Chloroquine, Remdesivir, Ivermectin, Lopinavir/Ritonavir, Favipiravir and therapies may include convalescent plasma therapy and corticosteroids.Hydroxyl-chloroquine and chloroquine exibites its action against SARS-COV-2 by blocking the entry of viral cell inhibiting glycosylation of host receptor Ivermectin show anti SARS-COV-2 action by binding of Ivermectin to the imp α/β1 binding to viral proteins. This particular action prevents the viral from entering the nucleus which leads to reducing inhibition and antiviral response. Remdisivir (G-S5734) is an RdRP polymerase inhibitor and exhibites anti SARS-COV-2 action by inhibiting viral nucleic acid synthesis. Patients treated with convalscent plasma therapy and corticosteroids gives less mortality rate and has no adverse effect .The speed and volume of clinical preliminaries propelled research expected treatments for COVID-19 feature both the need and capacity to treat excellent proof even in pandemic no treatment demonstrate effective to date.

KEYWORDS: COVID19, Hydroxychloroquine, Chloroquine, Ivermectin, Remdisivir, Lopinavir/Ritonavir, Favipiravir.

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INTRODUCTION:

In December 2019 A novel corona virus disease (COVID-19) Caused by infection with SARS-COV-2 has widely spread around the globe [1]. The first report of pathological characteristics of the patient who passed away from drastic infection with SARS-COV-2 Showed that an increased concentration of highly pro-inflammatory cytokinase. Actually the cytokinase storms moderated by overpopulation of critically afflicted patients infectd with COVID-19 Patients agonized leads to cardiovascular collapse multiple organ dysfunction and death rapidly. Therefore early recognition, therapy and precaution of the cytokine storms are of crucial importance for the patients [2].Coronaviruses (COVs) are enveloped RNA viruses related to the family coronaviridae six corona virus species are caused for disease in humans out of which only two viruses are able to caused acute respiratory syndrome coronavirus (SARS-COV) and Middle east respiratory syndrome (MERS-COV)[3]. In December 2019 many Pneumonia causes reported by patients with unknown causes, mainly associated with seafood and wet animal market in Wuhan, China And where clinically resembled viral pneumonia[4]. Currently there is no specific drug to treat COVID-19 and vaccine and new treatments could take years to fully developed, but the world health organisation recently launched a large international trail called Solidarity to test for existing therapies they are closely related Malaria drugs Chloroquine and Hydroxychloroquine, the antiviral

medication Remdesivir (Originally developed to treat Ebola) the antiviral combination of Lopinavir and Ritonavir (Used for HIV) and anti-inflammatory small protein interferon beta, a number separate clinical trail of these medication and other are underway in several countries all over the world [5].

Possible Drugs which are examined in the treatment of COVID-19 are:

CHOLOROQUINE AND HYDROXYCHLOROQUINE:

Since Long time hydroxychoroquine and chloroquine are used in the treatment of Malaria and chronic inflammatory erythmatosis and rheumatoid arthritis (RA), Chloroquine and hydroxychloroquine appear to block viral entry into cell by inhibiting glycosylation of host receptors proteolytic processing and endosomal acidification these agents also have immunomodulatory effects through attenuation and cytokine production and inhibition of autophagy and lysosomal activity in host cells.

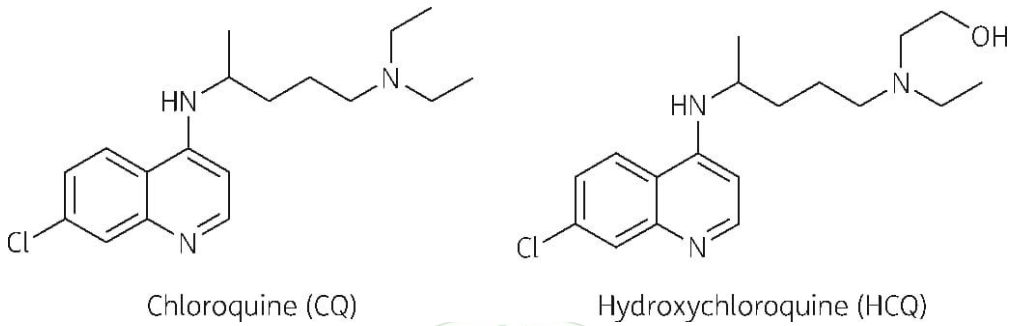

Figure 1:-Clinical Structure of Chloroquine and Hydroxychloroquine

The mechanism of action of hyroxycloroquine / Chloroquine against SARS COV-2 yet still not fully illuminate the effect of chloroquine and hydroychloroquine was firstly studied in SARS-COV which was responsible for the middle east respiratory syndrome (MERS-COV) 2002-2003 coronavirus epidemic SARS COV shows 79% genetic sequence similarity to SARS COV-2 Based on this studies initially performed on SARS- COV, It is believed that chloroquine and hydroxychoroquine plays important role in prevention and treatment of SARS COV-2 [7].Hydroxychoroquine is less toxic Aminoquinoline and has an N-Hydroxy Methyl side Chain in place of N-diethyl group of chloroquine this modification makes hydroxychloroquine more soluble than chloroquine [8]. It is considered that SARS COV-2 enter cells by binding to angiotensin converting enzyme 2 (ACE-2) receptor and that chloroquine may prevent the virus from binding to the receptor by inhibiting terminal glycolysation both hydroxyl chloroquine and chloroquine additioaly can incorporate into endosomes and lysosomes resulting in an increased Ph of intracellular compartments these organelles normally require an acidic environment for homeostasis . Eventually this increases in Ph result in their dysfunction leading to defective protein. Degradation endocytosis and exocytosis needed for viral infection and propagation previous work has also demonstrated that coronaviruses can use proteins on the surface of endosomes and endolysosomes for viral entry into host cells [9]. Entry into the endolysosomes may be necessary for the viral genome to be released into cytoplasm of infected host cells, however it remains unclear how changes in the endosomal environment particularly changes in Ph may affects the integrity of SARS-COV-2 viral genome overall, hydroxychloroquine and choroquine are capable of affecting several cellular pathways and therefore may have several mechanisms of action against SARS-COV-2[10]

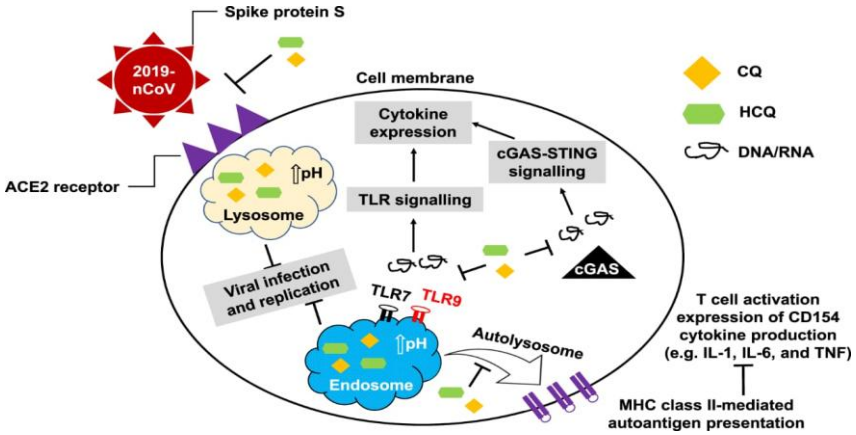

Figure: 2 Mechanism of action of Chloroquine and Hydroxycholoroquine against COVID-19

IVERMECTIN:

Ivermectin is a member of Avermectin family. As these particular compound produced form the soil micro-organisms strepomyces avermitilis . This compound shows wide range of antiviral, antibacterial an anti-cancer activity its mechanisms of action involves the opening of glutamate- gated Tebrates and GABA-gated chloride channel leading to increased conductance of chloride ions and causing subsequent motor paralysis in parasite [11]. Since, long time Ivermectin, used as an antiviral drug against human and animal viruses the first report of vivo effectiveness of Ivermectin against viruses demonstrated its effect against parvoviruses in a freshwater cray fish (Cherax quadricarinatus) as it posses endo/ecto parasiticide action hence it exibites action against several RNA viruses such as Zika virus, Influenza- A virus , Venezuelan equine, encephalitis virus. Etc[12].

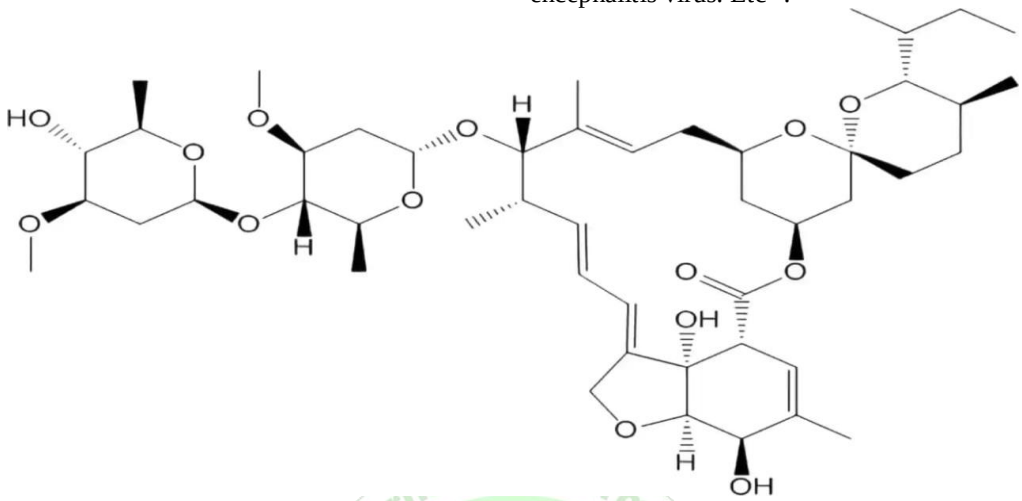

Figure: 3 Clinical Structure of Ivermectin

Ivermectin also exhibited antiviral action against deoxyribose nucleic acid (DNA) viruses such as Pseudorabies viruses, porcrine circovirus, parvo viruses and bovine-Herpesvirus out of this only pseudorabies exhibits antiviral potential of Ivermectin the broad-spectrum and antiviral potential of Ivermectin against several RNA and some DNA virus is due to its ability to specifically inhibit importin Alpha and Beta- mediated nuclear transport which inturn blocks the nuclear trafficking of viral proteins as SARS-COV-2 is RNA viruses is Expected to show same mechanism of action. The perposed of anti-SARS COV-2 action of Ivermectin involves the binding of Ivermectin to the imp alpha and beta heterodimer ,leading to destabilization and prevention of imp α /β1 binding to viral proteins. This particular action prevents viral proteins form entering the nucleus, thereby reducing the inhibition and antiviral response and leading to an efficient antiviral response [13]. According to study of Caly et al, vero-hsLAM cells where treated with Ivermectin after 2 hrs of SARS COV-2 infection resulting in ~5000 fold reduction in viral RNA after 48hrs, on the basis of all this studies and mechanism of action of drug, Ivermectin considered as useful drug in treatment and prevention of COVID-19 [14,15].

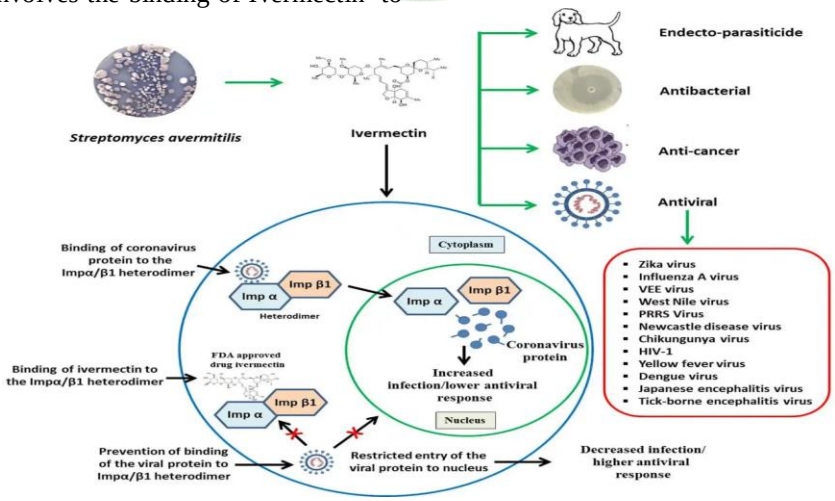

Figure: 4 Mechanism of action of IVERMECTIN

REMDESIVIR :

Remdisivir is also known as GS-5734 is a monohosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. This agent was found to amidst a screening process for antimicrobials with activity against RNA viruses such as Coronaviridae and Flaviviridae this agent showed a promising effect during the time of Ebola out break due to low EC50 (EC50 is the concentration of drug that give half-maximal

response) and host polymerase selectivity against Ebola Virus [16] . In current time Remdisivir showd promising effect in the treatment and prevention of COVID-19 because this particular agent has broad – spectrum and potent activity against several RNA viruses such as SARS-COV-2 with EC50 and EC90 (EC90 is with concentration of drug that gives 90% maximal response) values of 0.77 Micron meter and 1.76 micrometer respectively. A recent study demonstrates that Remdesivir efficiently inhibited SARS-COV-2 infection of human liver cancer Huh-7 cells which are sensitive to SARS-COV-2 infection. On the basis of recent study treatment of remdesivir on rhesus monkey for 12hrs, After inoculation of MERS-COV also provided a significant clinical benefit, signs reduces virus replication in respiratory tissues, and decreased occurance and severity of lung lesions [17].

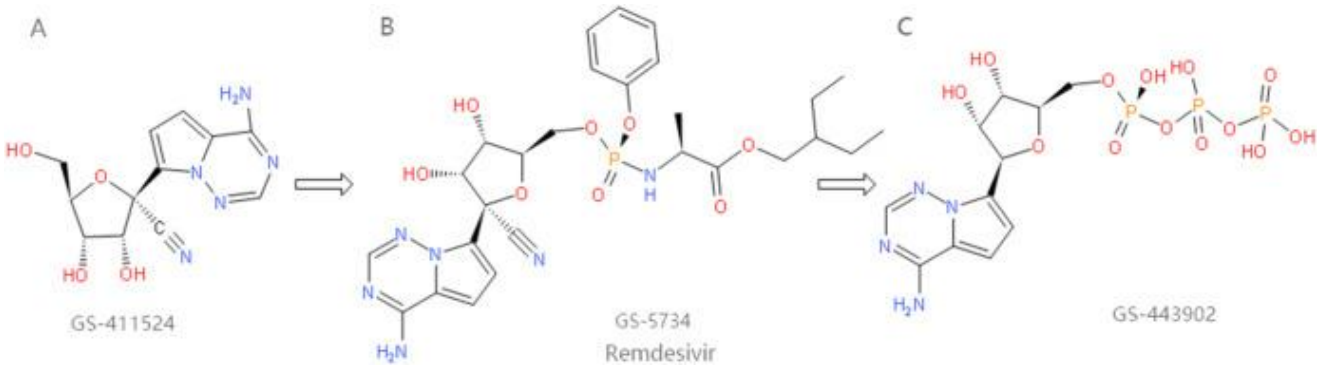

Figure: 5 Structure of REMDISIVIR and its precursors and metabolites

Remdesivir (GS-5734) is an RdRP (RNA- dependent-RNA polymerase) inhibitor and Exibites antiviral effect by inhibiting viral nucleic acid synthesis. COVID-19 is an Enveloped RNA Virus and genomic Replication of such RdRP inhibitors which is encoded by the virus itself. After the virus invades the host cell, the viral genomic RNA is directly used a template, and the host cell protein synthesis system is used for the translation of RdRp at the same time, RdRP under goes transcriptional synthesis of negative strand subgenomic RNA and replication of viral genomic RNA. RdRP can accurately and efficiently synthesis can accurately and genomic RNA-1RdRp can accurately and efficiently synthesis ten thousand of nucleotides and thus facilitates all other biological activities after the virus invades the host cells[18]. Remdesivir which is a monophosphoramidates prodrug of an adenosine analogue, enters the host cell in the form of prodrug is converted into nucleoside monophosphate (NMP)and then dephosporylated to active nucleoside triphosphate (NTP). NTP and ATP (Adenosine Triphosphate) have a similar structure and competitively bind to the viral RdRP with similar efficiencies. NTP is inserted into the RNA synthesis chain at position i through the recognition of RdRP and this process leads to RNA chain termination at a position few bases downstream of position i . This processs is called as chain termination and predominantly occurs at position i+5. Through this process, the replication of the virus is suppressed [19].

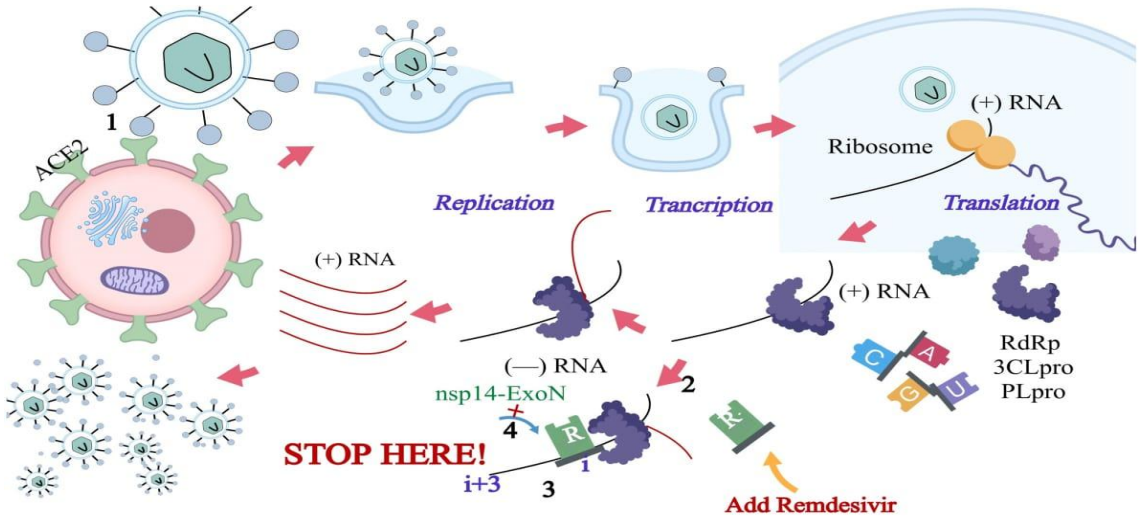

Figure: 6 Mechanism of action of REMDISIVIR against COVID-19

Lopinavir/Ritonavir:-

Lopinavir and Ritonavir are the protease inhibitors and protease inhibitors are the important agents in contemporary treatment of patients with chronic human immunodeficiency Virus (HIV) infection [20]. Lopinavir in particular an HIV-1 protase inhibitor, its combination with ritonavir has shown to be effective against SARS-COV-1. The combination of the two also reduced clinical scores and disease progression in animals infected with MERS-COV[21]. Previous studies showed the combination of lopanavir and ritonavir to be of some use for SARS-COV-1 and MERS-COV infected patients[22].Clinical studies in SARS-COV-1were associated with reduced mortality and intubation rates both the anti-HIV drugs interacted well with the residues at the active sites of SARS-COV-2 3CLpro [23]. Ritonavir showed a somewhat higher number atomic contacts, a somewhat higher bonding efficiency and higher number of key binding residues compared to Lopinavir, which corresponds with the slightly lower water accessibility at 3CLpro active site [24]. Adverse effect of Lopinavir/ Ritonavir Include gastro intestinal distress such as nausea and diarrhea, and hepato-toxicity [25].Cao and colleagues reported the results of an open- label randomized clinical trial comparing the efficacy of lopinavir/ Ritonavir versus standard care in 199 patients with COVID-19, time to clinical improvement was similar in both group no significant differences in viral clearance and in mortality rates was observed [26].

Favipiravir:-

Favipiravir triphosphate is a p[uine nucleoside analogue, which act as a cmpetative inhibitor of RNA dependent RNA Polymerase. Favipiravir(T-705;6-fluro-3-hydroxy-2-pyrazine carboxamide) is sold under the brand names AVIGAN,ABIGAN and FabiFLu, is an antiviral medication used to treat influenza in japan. It is also being studied to treat a number of other viral infections. Like the experimental antiviral drugs (T-1105 and T-1106), pyrazinecarboxamide derivative. It is being developed and manufactured by Toyama Chemical (Fujifilm group) and was approved for medical use in Japan in 2014 [28].

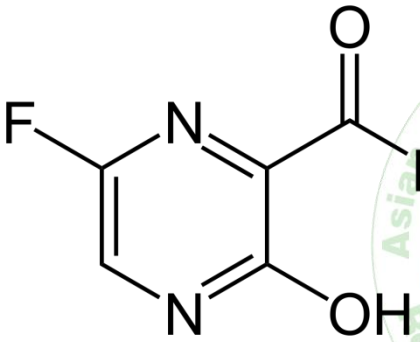

Figure: 7 Structure of Favipiravir

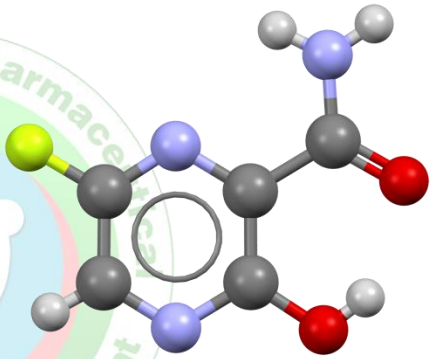

Figure: 8 Mercury 3D balls structure of Favipiravir

The mechanism of action is thought to be related to the selective inhibition of viral RNA-dependet RNA polymerase. Other research suggests that Favipiravir induces lethal RNA transversion mutations, producing a nonviable viral phenotype. Favipiravir is a prodrug that is metabolized to its active form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir RTP), available in both oral and intravenous formulations. Human hypoxanthine guanine phosphoribosyltransferase (HGPRT) is believed to play a key role in this activation process [26]. Favipiravir does ot inhibit RNA or DNA synthesis in mammalian cells and is not toxic to them. In 2014 , favipiravir was approved in Japan for stockpiling against influenza pandemics. However, Favipiravir has not been shown to be effective in primary human airway cells, casting doubt on its efficacy in influenza treatment. Favipiravir has activity against influenza-A and B, including activity against oseltamivir and zamnavir resistant influenza viruses, several agents of viral haemorragic fever and SARS-COV-2 In-vitro. Favipiravir was identified to have activity in-vitro against SARS-COV-2 albeit requiring a high concentration compared with chloroquine or remdesivir (EC50=61.88µm). Despite a similar elevated EC50 identified for favipiravir and Ebola virus it was identified in previous animal models to be highly effective as post-exposure prophylaxis for mice exposed to Ebola virus challenges, with rapid viriological response preventing mortality. Based on dosing strategies and pharmacokinetic data from human influenza trails, a intensified dosing strategy of 6000mg loading on day 1 followed by maintainence therapy of 1200mg orally twice daily for 1 days was employed in a single-arm clinical trail for Ebola virus disease in Guinea. In a retrospective analysis of 1247 patients with Ebola virus disease in Sierra bone. Those treated with favipiravir had a significally higher survival rate compared with patients receiving supportive management (56.4%) versus 35.3%; p=0.027) Patients received Favipiravir 800mg orally twice daily on day 1 and 600 mg orally teice faily on days 3-11 viral loads were quantified for 35 patients twice during their hospitalization and were significantly reduced amongst patients receiving favipiravir. Favipiravir has also been used as pharmacological post-exposure prophylaxis for Ebola virus disease. In a case series of four healthcare workers with higher risk Ebiola virus exposures, including two hollow hore needle stick injuries, none of the paitents who received 10 days of higher-dose favipiravir developed Ebola virus disease. Early clinical experience with Favipiravir for

COVID-19 is promising. A pen-label non-randomized trail of 80 patients with COVID-19 in China identified a significant reduction, in the time of SARS-COV-2 viral clearance in patients treated with favipiravir compared with historical controls treated with Lopinavir/ Ritonavir. Patients with mild or moderate COVID-19 were enrolled withn 7 days from disease onset, or critical disease, chronic liver disease or end-stage renal diosease were excluded patients in the intervention arm received favipiravir 1600mg orally twice daily on day 1 folowed by 600mg orally twice daily on days 2-14, Both arms were co-treated with inhaled IFN-αlb 60µg twice daily and therapy was discontinued until viral clearance, up to a maximum of 14 days. Thirty five patients were assigned to Lopinavir / Ritonavir, with a median age of 47 years (IQR=35.8-61);13.7% were ≥65 years old. There was a significant reduction in the maedian time to viral clearance with favipiravir (4 days ; IQR=0.5-9) compared with lopinavir/ ritonavir (11 days ; IQR= 8-10 p<0.001) further, by day 14. 91.4% of patients in the favipiravir arm had radiographic improvement versus 62.2% in the Lopinavir/ Ritonavir arm. There was a significantly lower rate of advers events in patients receiving favipiravir (11.4 % versus 55.6%; p<0.01) [27].

Possible Supportive Therapies:-

Convalscent Plasma therapy:-

Convalscent plasma therapy on immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite trearment with pulsed methyl prednisolone**.** Moreover , several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma therapy [29]. In year 2014,the use of convalescent plasma collected form paients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks a protocol for the use of convalescent plasma therapy in the treatment of middle east respiratory syndrome coronavirus was established in 2015. In terms of patients with pandemic 2009 influenza A H1N1 virus infection, prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality for patients treated with convalescent plasma [30]. Additionally in a subgroup analysis, viral load after convalescent plasma treatment was significantly lower on days 3, 5, and 7 after intensive care unit admission. No adverse events were observed. A multicentre, prospective double-blind, randomise controlled trail by Hung and colleagues showed that using convalescent plasma from patients who recoverd from the influenza-A H1N1pdmog virus infection to treat patients with severe influenza A H1N1 infection was associated with a lower viral load and reduced mortality within 5 days of symptom onset [31]. A meta- analysis by Mair-jenkins and colleagues showed that the mortality was reduced after receiving various dose of convalescent plasma in patients with severe acute respiratory infections, with no adverse events or complications after treatment another meta-analysis by Luke and colleagues identified eight studies involving 1703 patients with 1918 influenza pneumonia from 1918 to 1925 who received an infusion of influenza convalescent human blood product, which showed a pooled absolute reduction of 21% in the overall crude case- fatality rate at low risk of bias [32]. One possible explanation for the efficacy of Convalscent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia. Schoofs and collegues report that 3BNC117 mediated immunotherapy, which is a brand neutralising anti-body to HIV-1, enhances host humoral immunity to HIV-1. An in vivo trial also showed that the effects of this anti body were not only limited to free viral clearance and blocking new infection, but also included acceleration of infected cell clearance [33]. Viraemia peaks in the first week of infection in the most viral illness. The patient usually develops a primary immune response by days 10-14, which is followed by virus clearance. Therefore, Theoratically it should be more effective to administer the convalescent plasma at the early stage of disease, However, other treatments might have an effect on the relationship between convalescent plasma and antibody level, including antiviral drugs, steroids, and intravenous immunoglobulin [34].

Corticosteroids:-

Corticosteroids are commonly used for modulation of a variety of inflammatory conditions. In addition to a daily regimen, they can be used in the form of pulse therapy to treat flares of autoimmune diseases. However, caution in the use of corticosteroids is needed due to the potential serious side effects associated with corticosteroids drugs and that corticosteroids generally suppress the immune system. The latter means that corticosteroids modulate hyper inflammation and on the other hand, inhibit immune responses that are vital for the host defense against the virus [35].The study investigated the effect of inhaled corticosteroids ciclesonide, cortisone, prednisolone, dexamethasone, and fluticasone on the replication of the MERS-COV. Among the four compounds, the only ciclesonide was capable of inhibiting viral replication. Also, ciclesonide induced a significant inhibition of viral replication of other human coronaviruses, such as HCOV-229E and SARS-COV, and another positive-strand RNA virus, Rubella virus, while not effect the viral replication of negative- strand RNA virus, eg., influenza and respiratory syncytial virus for the MERS-COV, a non-structural protein 15 (NSP15) appeared to act as the target of ciclesonide [36] . An amino acid substitution in the NSP15 conferred resistance of the mutated MERS-COV-2, all three ciclesonide, mometasone could help deal effectively mutated MERS-COV for the SARS-COV-2, all three Ciclesonide mometasone and lopinavir were able to inhibit viral replication to similar degree [37]. Interestingly, Their effect was more noticeable than serine protease inhibitors, eg**,**Nafamostat and camostat in the cells that vero cells that express TMPRSS2. It indicates the tendency of the SARS-COV-2 to enter the cell through the cathepsin PER endosomal pathway rather than through the TMPRSS2 PER cell surface pathway [38].The study included 46 patients with severe COVID-19, of these 26 patients received methylprednisolone ad 20 patients received standard therapy without methyprednisolone [39]. The first group achieved faster improvement in clinical symptoms and lung lesions detectd by CT imaging. However, two deaths

occurred in the first group and one death in the second group. Moreover, the two groups did not differ in laboratory parameters, including WBC, lymphocyte count, monocyte count, and cytokines six days after treatment [40].

CONCLUSION:

The COVID-19 pandemic speaks to the greatest worldwide general well being emergency of this age and, conceivably, since the pandemic influenza outbreak of 1918. The speed and volume of clinical preliminaries propelled research expected treatments for COVID-19 feature both the need and capacity to treat excellent proof even in a pandemic no treatment demonstrate effective to date.

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