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COVID-19: VARIANTS, PATHOGENESIS AND TREATMENTS

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ABSTRACT

Novel coronavirus, commonly known as SARS-COV-2 (severe acute respiratory syndrome human corona virus 2), emerged in Wuhan, China, and spread catastrophically over the world. India is likewise dealing with the difficult issue of managing the viral outbreak and has managed its growth rate through certain severe restrictions. Covid19 is a harmful virus. Coronaviruses are a family of similar viruses that can infect the human respiratory system and result in anything from minor symptoms to fatal consequences. The main symptoms of the illness included the normal pneumonia, fever, dry cough, difficult breathing, and headache. The incubation period could last up to 14 days. We will summarizes and update the most popular medications used to treat COVID-19 in this review.

I. INTRODUCTION

The world health organization (WHO) declared COVID 19 as a global pandemic on March 11, 2020, after a novel coronavirus (COV) named '2019 –n COV' or 2019 novel coronavirus or COVID 19 due to named by crown like spike like on their surface by the world health organization (WHO). The covid 19 began in early December 2019 near Wuhan city, Hubei provinces China. (Harapan.H.et al,2020;Cascella.M.et al,2022) The top 10 countries with maximum number of infected cases are the united state of America, Spain, Italy, Germany, France, china, Iran , united kingdom, turkey and Switzerland . The first case was reported on 30th January 2020 in a female of Thrissur district , Kerala India having travel history to Wuhan state, china

(Rajan.G.U.P.T.A.et.al.2020;Yadav.D.et.al.2020)

A new and novel coronavirus (severe acute respiratory syndrome coronavirus -2, SARs – Cov-2) has just been found and defined as the cause of COVID -19. The clinical manifestation of COVID -19 can vary from asymptomatic and mild flu-like symptoms to acute respiratory distress syndrome and death. (Wu.R.Wang.et.al.2020;Li.Y.D.et.al.2020) the genome of the novel coronavirus SARs- COV-2 causing atypical pneumonia in human population. COVID -19 infection leads to disorders of the coagulation system with an increased risk of thrombosis and embolism. (Diener.HC.et al,2020;Yadav.D.et al,2020) initially the COVID-19 showed similar symptoms to SARs –COV with fever, dry cough , breathing difficulties , headache, fatigue. (Khan.M.A.et al,2020)

The first stage is an infection of the upper respiratory tract .the earliest signs of coronavirus illness (COVID 19) in infected persons appear on average 5 to6 days after infection 7 , with a 95% confidence interval spanning from 2 to 14 days. Pneumonia is the second stage, while the majority of patients only have slight fever and upper respiratory symptoms others develop pneumonia with or without symptoms most commonly dyspnea. Complication in the third stage, the median period from beginning of symptoms to acute respiratory distress syndrome (ADRS) was 9.0 days (8.0-14.0), mechanical ventilation was 10.5 days (7.0-14.0) and ICU hospitalization was 10.5 days (8.0-17.0) among the same 41 patients in Wuhan ,china. Exist us or healing is the fourth stage, in the Chinese trial death occurred 18.5 (15.0-22.0) days following the commencement of COVID19 infection .(Matricardi.P.M.et al,2020)

This new coronavirus is a coronaviridae virus with a positive signal stranded RNA genome. COV-2 belongs to the beta sub-group of coronaviruses, which are divided into four sub-groups: alpha, beta, gamma, and delta SARs (Khan.M.A.et al,2020;Wu.R.Wang.et al,2020). There is an urgent unmet need of interventions both for prevention and treatment of this disease and more than 500 clinical trials are ongoing in this regard at present no study with robust methodology have clearly demonstrated benefits of hydroxychloroquine for treatment, pre exposure prophylaxis in healthcare workers or post exposure prophylaxis in coronavirus disease-2019 (DhampalwarS.et al,2020). Antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir,

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umifenovir, favipivarir, and oseltamivir) as well as supportive medicines (ascorbic acid, azithromycin, corticosteroids, nitric oxide, IL-6 antagonists) and other agents are among the pharmaceuticals and therapeutic agents used (Invermectin, Interferons, Quinolones). (Wu.R.wang.et al,2020; Khan.M.A.et al,2020) until we have specific vaccines on therapeutic drugs targeting SARs-COV-2," repurposed" drugs that have been approved by the FDA in the VSA for other indications have been used to treat COVIS -19 patients. This review will summarize the most current pharmacotherapeutics prescribed in treatment of severe cases of COVID-19 pateints. (Wu.R.wang.et al,2020)

Polypharmacotherapy is another important aspect to evaluate in the old patient. in particular due to increased risk of drugs interaction and side effects due to polypharmacotherpy , great attention should be paid to the kind and the number of drugs to used for the treatments of COVID-19 in the older patients.(Cenderello G.et al,2020)

COVID -19 VARIANTs

1. Alpha (B.1.1.7)

The B.1.1.7 lineage was thought to be 30 to 50 percent more contagious than the original SARs –COV-2 strains when it first arose in the United Kingdom (UK) in late December 2020 (Cascella.M.et al,2022). It quickly spread over the world and became the prevalent variations in the United States. The alpha variants are largely the same as those previously linked with covid -19 , such as persistant cough and fever. However , fever people reported symptoms of anemia, a loss or change a sense of taste or smell in January 2021 when B.1.1.7 accounted for about 86 % of infection , than in November to December 2020, when it accounted for just 16 % (Katella.K.et al,2022)

2. Beta (B.1.351)

First reported in South Africa in December 2020 (Cascella.M.et al,2022). Beta variant is known to be highly transmissible SARS-Cov-2 variant. (Yadav. P.D.et al,2022) there is no indication that symptoms of the beta variants are any different to other covid variants. The variants is believed to be more transmissible than original Wuhan virus but it is not thought to lead to more severe disease. (Duong .D.et al ,2021)

3. Gamma (P.1)

First reported in brazil in early January 2021 (Cascella.M.et al,2022). The gamma strain possesses the same mutation in its spike protein as the alpha and beta strains, allowing it to connect to human cells more easily. however ,its not anywhere near as transmissible as alpha or delta' says even. (Duong .D.et al ,2021)

4. Delta (B.1.617.2)

First reported in India in December 2020. (Cascella.M.et al,2022) the delta variant appear to be the same as the original version of COVID -19. Their symptoms are more like those of a common cold, such as cough, fever or headache, with the addition of significant loss of smell. It soon spread throughout the world, until omicron took its place in mid- December. (Katella.K.et al,2022)

5. Omicron (B.1.1.529)

First reported in South Africa in November 2021. (Cascella.M.et al,2022) Omicron is more transmissible than delta and it was considered to be even more efficient spreaders of the disease. Difficulty breathing or shortness of breath, loss of speech or mobility, confusion, or chest pain are all signs of 'omicron' variants. (Katella.K.et al,2022)

PATHOGENESIS

SARS-COV-2, a single – stranded RNA-enveloped virus, targets cells through the viral structural spike (S) Protein that binds to the angiotensin – converting enzyme 2 (ACE2) receptor.(Sanders.et al,2020) In this virus, bats served as the natural reservoir and were the terminal host, with the palm civet and dromedary camel the intermediary host for SARs- COV.(Harapan.H.et al,2021) COV's four structural proteins ,S ,N ,M, and E enable the virus to gain access to host cell , the S protein is heavily N- glycosylated, the M protein is present as a dimmers in the virion, which maintains shape and the E protein, a transmembrane protein with an ion channel activity plays an important role in viral pathogenesis. (Sanders.et al,2020) This promotes the virus's assembly and escape from the host cell. The novel SARs –COV-2, like the original SARs – COV, employs the ACE2 receptor to assist viral entrance into target cells, resulting in down regulation of these receptors and increased

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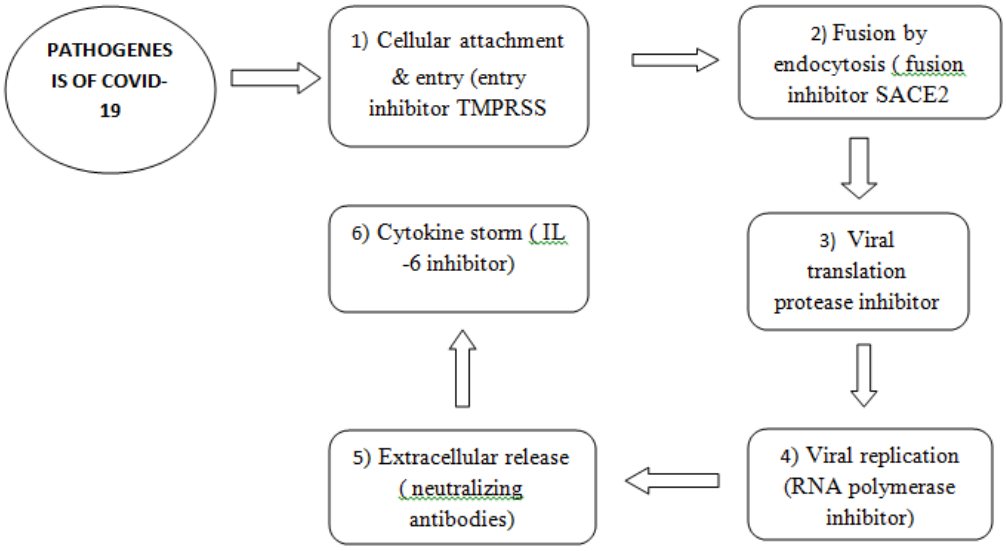
production of t –cells, which led to the patient's acute immunological damage. (Ochani.R.et al,2021). The incubation period for this virus ranges from 2 days 14 days with an average of 5 days for the onset of symptoms (Agarwal.K.M.et al,2020). The viral cycle is like other viruses consisting of attachment, integration, uncoating use of host cell machinery for replication, assembly and finally release of virions. Steps in corona virus replication are potential targets for antiviral drugs and vaccines.(Behera.S.S.et al,)



TREATMENTS

For COVID – 19 , there is no specific treatment available. The WHO announced the organization of a trail dubbed the "solidarity" clinical trials for COVID-19 treatment (Keni.R.et al,2020). During the pandemic that is causing morbidity & mortality to grow exponentially, there is an understandable temptation to make unproven therapies widely available and not wait for rigorous clinical trials data. At least 25 drugs are under investigation for used in COVID-19 , with 10 in active clinical trials. The first published major randomized , controlled trails of an antiviral drugs combination (lopinavir-ritonavir) began enrolling patients in china just a week after the virus had been indentified.(Rome.et al,2020

ANTIVIRAL AGENTS

REMDESIVIR

Remdesivir is a broad- spectrum antiviral agents that previously demonstrated antiviral activity against SARs-COV-2 in vitro(Cascella.M.et al,2022). Is formally known as GS-5734 is a monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. (Sanders.et al,2020) It is processed by the host cell into an active nucleoside triphosphate. In the case of SARs-COV, MERs, and Ebola, remdesivir inhibits the viral RNA dependent RNA polymerase (RdRp), producing delayed RNA chain termination, and it has been demonstrated that this medicine is effective against these viral outbreaks. (Khan.M.A.et al,2020) several clinical trials are going on to evaluate the effectiveness as well as the safety of remdesivir in COVID-19 patients recently , the US FDA has approved remedesivir as an emergency use for COVID -19 patients (38). Remdesivir is FSA approved (12 yrs and older and weighing at least 40 kg) to treat COVID -19 requiring hospitalization(Smith.T.et al,2020) a study of use of remedesivir reported clinical improvement of 68% by clinicians across nine different countries (Birkhoelzer.S.M.et al,2021)

CHLOROQUINE & HYDROCHLOROQUINE

Chloroquine (CQ) & hydrochloroquine (HCQ) structurally similar weak lipophilic base with a hydroxyethyl group in hydrochloroquine in place of ethyl group of chloroquine (Dhampalwar.S.et al,2020). CQ& HCQ are drugs with a long history of clinical use which used in treatment of rheumatoid arthritis and malaria (Wu.R.Wang.et al,2020). Chloroquine & hydrochloroquine used in the COVID- 19 due to the anti inflammatory & antiviral effects of both an international multi – centre analysis, subsequently retracted , investigated the use of HCQ and CQ with or without macrolides for the treatment of COVID -19(Stasi.C.et al,2020). The mechanism of chloroquine includes inhibition of viral enzyme or processes such as viral DNA and RNA polymerase, viral

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protein glycosylation, & virus release (Smith.T.et al,2020). Both drugs are inexpensive and safe but can cause gastrointestinal intolerance & risk of QT interval (QTC) prolongation leading to potential lethal arrhythmia(12)USFDA gave emergency approval to hydroxychloroquine and chloroquine in march 2020 (FDA2020) , several clinical trials were also undertaken to understand the effectiveness of this drugs in treating COVID-19 patients. In some clinical trials, hydroxychloroquine wad used to treat to COVID-19 patient alone or with a macrolide antibiotic, azythromycin. (Chakraborthy.et al,2021) long term daily use of hydroxychloroquine in pregnancy is non teratogenic, however, this conclusion is based on small case series.(Donders.F.et al,2020)

LOPINAVIR/ RITONAVIR

Lopinavir a peptidomimetic molecule is a protease inhibitor. Lopinavir is administered exclusively in combination with ritonavir (Behera.S.S.et al,) the brand name of such a combined drugs is kaletra, which displays a broad- spectrum antiviral activity including on SARs- COV- 2. Mechanism studies suggested that the lopinavir / ritonavir combination may inactive the 3- chymotrypsin – like cysteine protease (3cl pro) that cleaves protein precursors into a variety of active proteins required for the life cycle of SARs-COV-2 (Huang.L.et al,2020) It have most common adverse effect are gastrointestinal.(WHO.et al,2020) notably treatment with LPV/ RTV alone (400/100mg) administered orally twice daily for 14 days (Jean et al,2020). In vitro studies indicated activities of darunavir protease inhibitor and integrase strand transfer inhibitors against CoVID-19 (39) lopinavir /ritonavir is currently not indicated for the treatment of COVID-19 in hospitalized and non hospitalized patients (Cascella.M.et al,2022)

FAVIPIVAVIR

Favipivavir was discovered through the screening of a chemical library for antiviral activity against the influenza virus by the Toyama chemical co.ltd. But chemical modification of a pyrazine analog in carbaxamide derivative. It was approved for medical use in Japan, in 2014, for the treatment of the new or remerging pandemic influenza virus infections (Joshi.et al, 2021) the prodrug favipiravir first enters the infected cells through endocytosis and is then transformed into active favipiravir ribofuranusyl phosphorylation. Recent in vitro and human studies have repurposed favipivavir as an experimental agents against enveloped , positive sense single- strand RNA virus SARs- COV-2 (Wu.R.Wang.et al,2020) It inhibits viral RdRp and the system used in antiviral screening is viro E6 cells .(De.P.Chakraborthy.et al,2021) Clinical recovery with favipivavir in patients with COVID -19 shown to be slightly faster 61% than arbidol 52% and it shows some adverse effects also about 11.43% of patients have been reported to have adverse effects including nausea, diarrhea, rash and chest tightness with favipivavir treatment.(Khan.M.A.et al,2020)

IMMUNOMODULATING AGENTS

AZITHROMYCIN

Azythromycin is have immunomodulators and anti-inflammatory properties is well established as a potent treatment for some skin diseases such as psoriasis and acne.(Tursen.U.et al,2020) The system used for screening in COVID-19 patients in hospitals is (clinical trials) to study combination of CLQ-OH (200 mg thrice daily) plus Azithromycin (500 mg on day 1) followed by 250 mg once daily on day 2-5) showed excellent clinical efficacy on Chinese COVID-19 potency patients and anti SARs-COV-2 potency in vitro (Khan.M.A.et al,2020). Hydrochloroquine and azithromycin both agents are known to prolong the QT interval and may potentiate the risk for cardiac events in a population known to have cardiac related co morbidities (Wu.R.Wang.et al, 2020)

CORTICOSTEROIDS

Severe COVID-19 is associated with inflammation related lung injury driven by the release of cytokines characterized by an elevation in inflammatory markers during the pandemic early course, glucocorticoids efficacy in patients in patients with COVID-19 was not well described (Cascella.M.et al,2022). The UK RECOVERY trial assessed the mortality rate at day 28 in hospitalized patients with COVID-19 who received low dose dexamethasone 6mg Po or 4 daily for 10 days added to usual care. An association between corticosteroids & reduced mortality was similar for dexamethasone & hydrocortisone, suggesting the benefit is a general class effects of glycocorticoids (Bergman.S.J.et al,2021) appropriate & short term use of corticosteroids to inhibit

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cytokine cascade & to prevent disease progression should be COVID-19 pneumonia as early as possible. Initial routine methylprednisolone at a dose of 0.75-1.5 mg/kg intravenously once a day is recommended. Methylprednisolone at a dose of 40 mg -80 mg q 12 h can be considered for critical cases (Liang.T.et al,2020)

OTHER AGENTS

IVERMECTIN

Ivermectin is an FDA approved anti parasitic drug used worldwide in the treatment of COVID-19 based on an invitro study that showed inhibition of SARs-COV-2 replication.(Cascella.M.et al,2022) Ivermectin prevent viral protein to either into host cell nucleus by binding with IMP alpha and beta 1 . Ivermectin in combination with CLQ-OH and antiretroviral medicines (ART) (NC-T04435587) is in phase 4, while a nitazoxanide, ribavirin, and ivermectin combination (NCT04392427) is in phase 3. (Khan.M.A.et al, 2020) Additional research shows that it has the capacity to block viral reproduction in a wide range of viruses, including dengue virus, flavivirus, and influenza.(Wu.R.Wang.et al,2020)

INTERFERONS

Interferon's (IFNs) are a major category of cytokines, which are a part of our innate immune system. IFNs can be divided into two major groups' type 1& type 2. Type 1 IFN, namely , IFN-beta had been successfully tested in vitro to treat SARs-COV- infection, while IFN does not have any activity against the replication of SARs-COV.(38) clinical trials of IFNs are in phase2-4 trials NCT04343768, NCT04276688, NCT04350281 (phase2), NC-T04349410(phase3) CT04291729 (phase 4). (Khan.M.A.et al, 2020)

Anti-infective therapy with intracellular activity

Combination therapy recently demonstrated some potential for COVID-19 patients. According to certain studies, multidrug or combination therapy for COVID-19 outpatients may cut hospitalization and death by about 85%. Combination therapy has occasionally had remarkable outcomes when used to treat COVID-19 individuals. However, various life-threatening symptoms, including thrombosis, cytokine storm, and virally-mediated organ destruction, were seen in patients with severe COVID-19. In light of this, have determined that combination/multidrug therapy is an important consideration for treating COVID-19 individuals with serious illnesses**. (**Chakraborthy.et al, 2021)

The compelling rationale for prompt therapy is to minimize the degree of direct viral injury to the respiratory epithelium, vascular endothelium, and organs. SARS-CoV-2 infection is associated with severe disease and increased mortality in patients over age 50 years and those with one or more co morbidities, clinicians should use of at least two commercially available, anti-infective agents where it is appropriately considered clinically indicated, medically necessary "off-label" prescription.(McCullough.et al,2020).

Drug Toxicity During the Clinical Trials

Thousands of clinical trials are being performed to understand the safety and efficacy of the repurposed drugs for COVID-19. Some drugs have shown drug toxicity during clinical trials. (Chary.et al,2020) .Several studies have reported hydroxychloroquine and chloroquine toxicity; specifically, cardiovascular toxicity has been observed in several cases. Drug-drug interaction is a problem for co morbid COVID-19 patients, which might generate toxicity. It has been noted that anti-SARS CoV-2 drug candidates might have interactions with hepatic transporters. Therefore, this can cause liver toxicity.(chakraborthy.et al,2021).

II. CONCLUSION

The medications and vaccine against SARS-COV-2 to combat COVID-19 are currently a big challenge. Health professionals all over the world are working hard to identify the finest medications or medication combinations that have the fewest side effects. Medications such as favipiravir, remdesivir, lopinavir and ritonavir combined, hydroxychloroquine and azithromycin combined, ivermectin, corticosteroids, and interferon, among the others.

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