CURRENTLY AVAILABLE DOSAGE FORMS AND THE ROUTE OF ADMINISTRATION OF DRUGS FOR COVID-19 TREATMENTS

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of B.Sc. in Pharmacy.

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Declaration

I hereby declare that

1. The thesis presented is my original work completed while pursuing the Bachelor of pharmacy at Brac University.
2. 2. The thesis does not incorporate anything previously published or generated via any third party, unless it is correctly cited through extensive and exact citing.
3. The paper does not include any content which has been authorized or presented for a degree or certificate from another institution or university.
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Approval

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Ethics Statement

This paper does not include any animal or human experiments.

Abstract

COVID-19 has been labeled a worldwide pandemic in 2020. The mortality rates have raised rapidly due to restricted treatment options. The COVID-19 outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is continuously expanding. In the pathophysiology of this illness, the patient's immune response is crucial. In extreme cases, the mediators of this inflammatory factor were shown to reach the cytokine at maximum amounts. Due to alterations in drug pharmacokinetics, a hyperinflammatory state can produce severe anomalies in transporters and drug metabolic machinery, resulting in unforeseen therapeutic responses. The present situation considers the necessity for medications to treat to alleviate and eliminate the epidemic. COVID-19 continues to spread internationally amidst global deployment of precautionary measures to fight the illness. Some of the medications for COVID-19 are: Remdesivir (Veklury), Bebtelovimab, Molnupiravir (Lagevrio), Nirmatrelvir with ritonavir (Paxlovid) etc.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); acute respiratory disease syndrome (ARDS); pathology; immunopathology; COVID-19, Drug transporters, CYPs , Remdesivir, Dexamethasone Molnupiravir.

Dedication (Optional)

Dedicated to my family and friends

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Table of Contents

List of Tables

List of figures

List of Acronyms

AGP Aerosol-Generating Procedure*

ACE2 Angiotensin Converting Enzyme 2

AIIR Airborne Infection Isolation Room

APF Assigned Protection Factor**

APR Air-Purifying Respirator (particulate respirators, gas masks)

ARD Acute Respiratory Disease

ARDS Acute Respiratory Distress Syndrome

ASR Air-Supplying Respirator

CAPR Controlled Air Purifying Respirator

FFR Filtering Facepiece Respirator (includes N95 masks)

HCP Health Care Personnel***

NIOSH National Institute for Occupational Safety and Health

PAPR Powered Air Purifying Respirator

PPE Personal Protective Equipment

Pgp P-glycoprotein

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2

Chapter 1

Introduction

1.1 Background

Corona viruses were identified in the 1960s. Because of how they appear under an electron microscope, they are positive-stranded RNA viruses known as "crowns." Humans, along with certain animals, can be infected. The infections caused by the alpha and beta coronaviruses range from common colds to serious disorders in respiration. Beta corona viruses are the most common cause of these problems: Mers-Cov.1–3; SARS-CoV. During 2019 (December), the Wuhan area of China announced the first instances of infection caused by a new coronavirus of humans. The International Committee on Virus Taxonomy (ICTV) gave the novel coronavirus a name: "Severe Acute Respiratory Syndrome coronavirus 2" (SARSCoV-2). A committee of scientists in charge of researching the novel coronavirus strain came up with the name. The new coronavirus, according to this group of experts, is related to the virus which generated SAR, thus the name SARS-CoV-2. A pandemic was announced in March 2020 by the WHO. According to the literature, COVID-19 may be treated with antimalarial and antiviral medicines, corticosteroids, monoclonal antibodies, antibiotics, and LMWH (low molecular weight heparin) from progressing to the severe inflammatory stage, which can lead to respiratory problems, multiple organ collapse, disseminated intravascular coagulation (DIC), and eventually death (Valentini & Zmerly, 2020). Our study's purpose is to examine justification and rationale for using antirheumatic medicines at different stages of illness, as well as to

detect those who are at elevated danger., in order to modify their lifestyles and improve their health through non-pharmacological approaches (Valentini & Zmerly, 2020).

In 2020, COVID-19 was declared a worldwide epidemic. With few treatments, its mortality and morbidity rates are quickly rising. The COVID-19 epidemic due to SARS-CoV-2 continues expanding (Kumar & Trivedi, 2021). The immunological response of the patient is crucial in the pathologic process of this infection.

1.2 Aim of the project

For the last 2 to 3 years, COVID-19 has posed a severe danger to the whole planet. Thousands of people died due to this disease. So here, we will focus on the currently available doses forms of COVID-19 as applying the correct doses forms for the right patients is very essential to save a life as it can directly affect the lungs and can be deadly. We will also discuss about the route of administration of drugs such as: oral, inhalation, parental for COVID-19 treatments as the route of administration varies from patient to patient and also what the drugs available for the COVID-19 treatments are. So, research paper is based on all of the above mentioned things.

1.3 Objectives of this study

The four main objectives of this study are:

- To describe the steps of COVID-19 diagnosis and patient.
- To enlist the available medications or dosage forms for the treatment of COVID-19.

- To discuss the risk and evaluation of diseases with drug and drug interactions in COVID-19 patients.
- To explain the mechanism of action of the potential drugs for the treatment of COVID-19 patients.

1.4. Significance

Development of the innovative antiviral medications to combat COVID-19 is an absolute necessity. The FDS (Food and Drug Administration) has authorized various drugs that have already been used to treat SARC-CoV and MERC-COV based on the data. In these investigations, favipiravir and remdesivir and showed the most potential versus COVID-19. The antiretroviral (ARV) medicine lopinavir was used with ritonavir for COVID-19 (potent anti-HIV drug). COVID-19 was shown to be resistant to the combination of ritonavir lopinavir. The antimalarial medicine hydroxychloroquine has shown to be more effective against COVID-19 and is used more frequently. Fluid management, oxygen support as needed for the patient's state, and antibiotics in the event of a subsequent infection are all recommended. To identify and prevent the spread of the virus, we need detection kits for diagnostic, vaccinations for long term protection, therapies to save lives in the near future, and social science to comprehend the psychological and social consequences.

Chapter 2

Methodology

We conducted a comprehensive literature analysis of the clinical characteristics and therapies for the novel COVID-19 using internet databases. We looked for relevant publications in Google Scholar, MEDLINE, UpToDate, PubMed, Web of Science and Embase, using the keywords COVID-19,''2019-nCoV,'coronavirus,' and 'SARS-CoV-2.' From January 1, 2019 to April 3, 2020, we included scientific articles. Only articles concentrating on SARS-CoV-2 clinical features and treatments were considered for inclusion. We looked through all of the references in relevant research to see if there were any publications that were missing. Two investigators worked separately to conduct all research, title and abstract filtering, and study selection. Any differences were handled through consensus. For full-text review, all papers considered possibly eligible were obtained. We confined our search to English-language publications, excluding conference abstracts and commentary (Pascarella et al., 2020).

Chapter 3

3.1 COVID-19 diagnosis and management

SARS-CoV-2, a new corona virus from the same family as SARS-CoV and MiddleEast respiratory syndrome corona virus, has spread over the world, prompting the World Health Organization to declare a pandemic (Pascarella et al., 2020). COVID-19 which is an illness triggered by SARS-CoV-2 has flu-like symptoms and can be fatal in risk patients. From the 1st of January 2019 through the 3rd of April 2020, the focus was on clinical aspects and therapies. Infection is spread from person to person and through contact with infected environmental surfaces, according to our findings. To avoid infection, proper hand hygiene is essential. In some situations, it is necessary to wear personal protection equipment. Fever, cough, lethargy, minor dyspnoea, sore throat, headache, conjunctivitis, and gastrointestinal problems are the most common symptoms of COVID-19. Nasal swab, tracheal aspirate, or bronchoalveolar lavage samples are used as diagnostic tools for real-time PCR (Pascarella et al., 2020). The results of computed tomography are crucial for both diagnosis and follow-up. So far, no effective therapy for COVID-19 has been discovered. Antiviral medicines, chloroquine/hydroxychloroquine, and respiratory therapy are the most common treatments for the infection. In conclusion, despite several therapies being recommended, quarantine appears to be the only intervention that appears to be helpful in reducing the rate of transmission (Pascarella et al., 2020). To find the most appropriate evidence-based therapy method, specially designed randomized clinical trials are required (Pascarella et al., 2020).

3.2. Virus transmission and epidemiology.

The virus's conceivable method of interspecies transmission is still a mystery. SARS-CoV-2 has been identified by many research organizations as a member of the β-corona virus family, having a genome that is almost identical to that of bat corona

virus. According to these findings, bats might be the virus's natural host. The newest coronavirus mostly infects the lungs and uses the exact like receptor as SARS-CoV [ACE2)]. Airborne transfer from one person to another is the most common form of infection, which occurs most often via infected hands, fluids, or surface. After a median incubation time of 2 to 12 days (5.1 days median) virus particles present in an infected person's respiratory secretions infect others by direct contact with mucosal membranes Virus transmission by asymptomatic or sick persons has been well described during the incubation phase. MERS-CoV and endemic human coronaviruses, for example, can persist for up to 9 days on surfaces like metal, plastic or glass, but can be effectively inactivated in 1 minute using 62–71 percent ethanol, 0.1 percent sodium hypochlorite or 0.5 percent hydrogen peroxide, according to a review of 22 studies (Pascarella et al., 2020). Furthermore, the majority of the information suggests that a social distance of 1.5 meters is sufficient to avoid airborne transmission. Transmission appears to be feasible for around 8 days after symptoms start. Patients may have a positive pharyngeal swab for many weeks after elimination of signs, although active virus cannot be found beyond roughly eight days illness, indicating that extended PCR (Polymerase Chain Reaction) test positivity is unlikely to correspond with the clinical transmission (Pascarella et al., 2020). The Centers for Disease Control and Prevention's guidelines does not specify how long patients should be isolated. It is permissible to assume that isolation is no longer necessary after 2 successive negative real-time (RT)-PCR tests separated by minimum 24 hours and in the absence of significant clinical or epidemiologic circumstances. (Pascarella et al., 2020). However, given the high likelihood of false-negative throat swab findings, this

proposal should be approached with care. The practical solutions below may help to reduce the probability of diagnostic mistakes. First, by integrating medical proof with data from CT (Chest Computed Tomography) and reverse transcription polymerase chain reaction (RT-PCR), diagnosis accuracy may be increased. (Pascarella et al., 2020). Second, in individuals who have a null RT-PCR but a strong likelihood of infecting, RT-PCR findings should be evaluated based on epidemiological and clinical tests. According to current statistics, the median number of people one infected person may infect [(R0) reproduction number] is 2.5–2.9. R0 shows the virus's pathogenicity as well as the number of social interactions and mixing patterns among the population that are crucial to the disease's spread (Pascarella et al., 2020). Specific contexts and circumstances should be recognized as having a higher risk of viral transmission, with transmission in health facility contexts being particularly significant. In Wang et al's case study, 57 of the 138 infection emerged in hospital environments, with 40 people among them involving health care professionals. In Italy, Spain, and the United States, residential and nursing homes, as well as other communal housing facilities, were responsible for local disease clusters (Pascarella et al., 2020). In order to reduce the danger of infection, general hygiene procedures are essential. Masks, eye protection gloves, and gowns are also suggested, especially for health workers. Furthermore, due to quarantining or isolation, the numbers of medical providers would severely overburden the system of healthcare. The main symptom of COVID-19 occurs within the exposure of 14 days; however, symptoms usually appear after about 5 days, and 97.5 percent of people have symptoms by 11.5 days (Pascarella et al., 2020).

This epidemic had a cumulative attack rate of 0–11 percent in China. COVID-19 has a 50-fold greater cumulative attack rate than influenza H1N1, which shares the exact transmission mechanisms. This emphasizes significance of quarantine and social distance measures, which has been implemented by governments across the world. Isolation is still the most effective approach for controlling COVID-19 spread. Containment of the epidemic should, in our opinion, be the primary goal of COVID-19 therapy, short-term containment costs and radiological considerations (Pascarella et al., 2020). Here's a figure of the transmission and epidemiology of the virus:

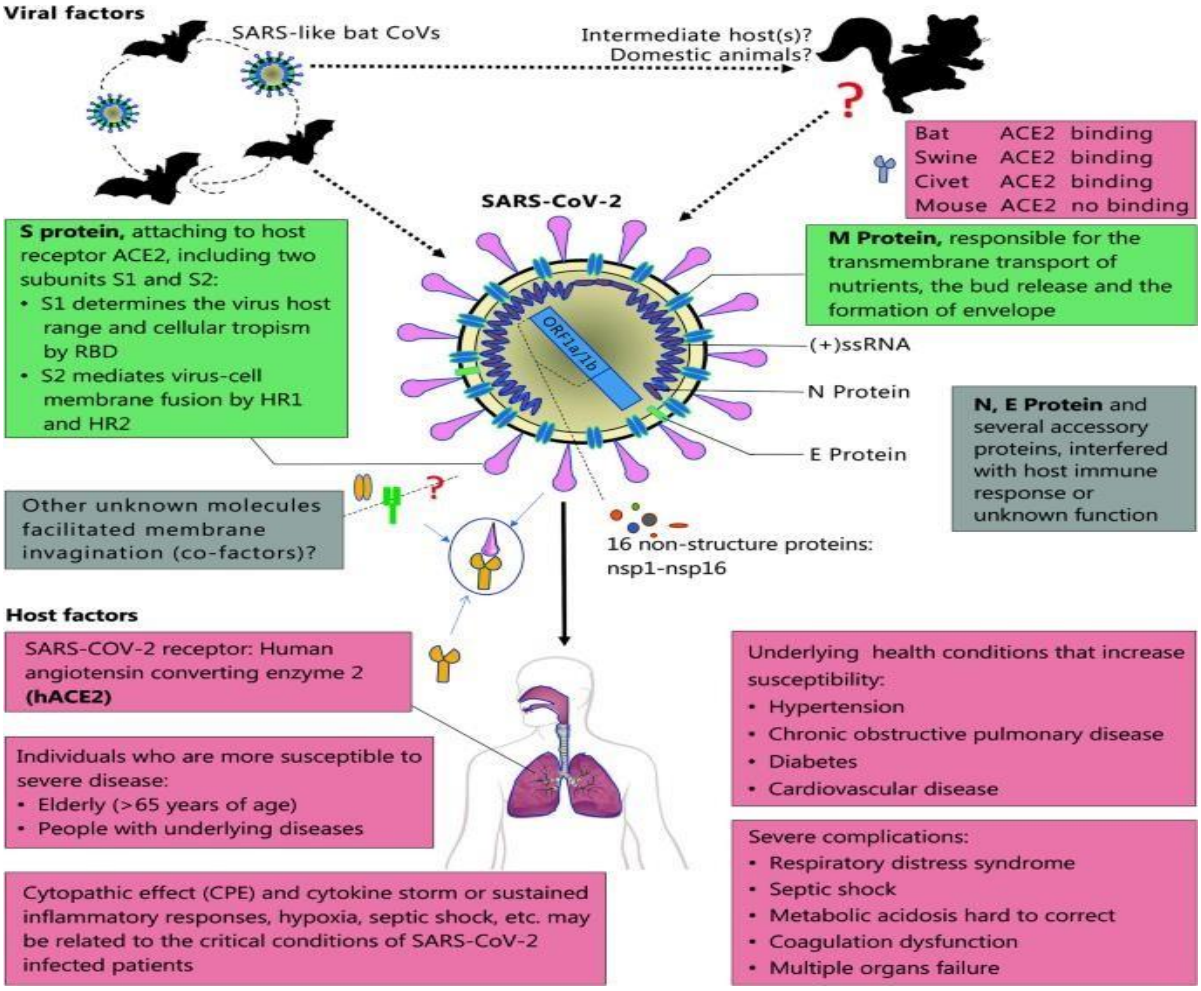

Figure 1: *The origin, transmission, epidemiology and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak* (Pascarella et al., 2020).

3.3. COVID-19 symptoms, course and prognosis

3.3.1

Symptoms

COVID-19 symptoms vary by person, ranging from asymptomatic illness to severe respiratory failure. Dr. Lavezzo and colleagues conducted an Italian demographic randomized trial in Vo Euganeo.in 2020 (unpublished data), which found that around 50 to 75 percent of people with positive RT-PCR findings are asymptomatic, whereas other have slight flu like symptoms. Around 10% of all symptomatic patients develop ARDS, dyspnoea, severe interstitial pneumonia and multi-organ dysfunction. The great majority of people with symptoms and more severe clinical patterns had one or more coexisting medical illnesses, such as cardiovascular diseases, diabetes, hypertension, and fatality of old and weak patients had higher cases (Pascarella et al., 2020). Fever, cough, weariness, minor headache, sore throat, dyspnoea, and conjunctivitis are all common signs of the disease. As a result, distinguishing COVID-19 from other respiratory disorders is challenging. Involvement of gastrointestinal was recorded in a small number of patients, with vomiting, nausea and diarrhea being the most common symptoms. SARS-CoV-2 may have neuroinvasive capability, according to Li et al., since some people may suffer respiratory failure as a result of viral infection of the central nervous system. Individuals with COVID-19 have reported hyposmia and dysgeusia, which could imply a virus neurotropism, which could infect the sensory fibres or, alternatively, the olfactory nerve and bulb, which innervate

various organ systems of the respiration pathway from the brainstem, including the lungs, trachea, and larynx. (Pascarella et al., 2020).

3.3.2

Course

SARS-neuroinvasive CoV-2's potential, on the other hand, remains a mystery and more research is needed. In around 80–90 percent of patients, the infection is moderate or asymptomatic. It is to note that around 10% of cases progress to seriousness, with dyspnea, hypoxia, and substantial (>50%) radiographic involvement of the lung parenchyma (Pascarella et al., 2020).

3.3.3

Prognosis

Multiorgan failure, shock, pneumonia, respiratory failure and in the most extreme instances, fatality usually happened due to progress to multi-organ failure and ARDS, develop in around 5% of cases (Pascarella et al., 2020). It has also been observed that people can acquire respiratory failure without experiencing dyspnoea ('silent hypoxaemia'). Hypocapnia due to compensatory hyperventilation is a common finding in these instances. The mortality rate varies between studies, ranging from 2% to 5%; the variation is likely due to differences in patient characteristics and/or the rate of prevalence of infection, and is influenced by corresponding count of number of diagnostic tests carried out on affected people (Pascarella et al., 2020). It is likely that quick saturation of critical care-facilities, particularly in epidemic hotspots, influenced fatality rates (Pascarella et al., 2020).

3.4.

Radiological findings

Ground glass opacities, notably in the lower lobes and peripheral, as well as bilateral multiple lobular and sub segmental foci of consolidating, especially in the patients of ICU, were common CT findings in people with COVID-19 (Pascarella et al., 2020). The proportion of lung segments affected was shown to be related to the severity of the illness. These opacities seemed to merge together and deepen as the sickness progressed. Pleural effusion (only around 5% of the time), masses, cavitations, and lymphadenopathies were all non-typical CT abnormalities, suggesting alternate diagnosis. The duration between the beginning of symptoms and the first CT scan was examined in one research, and authors discovered that 56% of the patients whom showed symptoms inside two days had usual CT pictures. Sensitivity of CT appear soaring in patients with a positive RT-PCR (In various cases 86% to 97%) but low in individuals having solely constitutional, non-respiratory symptoms (around 50 percent) (Pascarella et al., 2020). The sensitivity of traditional chest X-rays is roughly 59 percent. Only a few instances has ultrasound used as a diagnosis. It has a relatively low specificity, and its sensitivity is believed to be approximately 75%, though being impacted by variables like the severity of the sickness, the size of the patient, and the operator's skill. Ultrasound however, plays a role in monitoring the illness's course by detecting interstitial lung disease signs including B lines and subpleural consolidations (Pascarella et al., 2020). On ultrasonography, it exhibits three distinct interstitial presentations in patients. CT and ultrasound results are similar; CT appears to be more accurate in identifying apical intraparenchymal

lesions, but ultrasonic may detect even the smallest and pleural effusions and subpleural lesions (Pascarella et al., 2020). When a linear probe is used, sensitivity for subpleural lesions improves. With a dynamic air bronchogram, the principal ultrasonography findings show solitary or confluent B lines, as well as uneven or interrupted pleural line thickening (Pascarella et al., 2020).

Chapter 4

Antirheumatic medications for the medication of COVID-19 based on stages of illness

COVID-19 is most recent pandemic, having killed over 300,000 individuals and infected over four and a half million people. In terms of causation, treatment, and prognosis, it is an extremely complicated systemic disease. To prevent the condition from advancing to a severe inflammatory phase antibiotics, antimalarial and antiviral medications, corticosteroids, monoclonal antibodies, and low-molecular-weight heparins may be used which can result in respiratory complications, failure of multiple organs, disseminated intravascular coagulation and fatality. As a result, a comprehensive strategy to combating the illness is required until the much-desired vaccine is developed. It's important to use many medicinal therapies at the proper pathologic period. G purpose of the report is examining the logic with justification for using antirheumatic medications at various stages of the disease from the perspective of experts.

Another essential part of disease management is identifying individuals at high risk and working with them to adjust their lifestyles and correct their health using non-pharmacological approaches to improve their immune balance. Our assessment of the literature demonstrates the critical significance and therapeutic potential of antirheumatic drugs in limiting disease progression and assisting recovery. However, because there is a shortage of data to validate the application of these medications, further randomized controlled trials are needed (Valentini & Zmerly, 2020).

4.1. Antimalarial Drugs.

Since 1940, chloroquine and hydroxychloroquine have been used to treat autoimmune inflammatory rheumatism (Valentini & Zmerly, 2020). Hydroxychloroquine has a superior safety profile than chloroquine in terms of probable adverse effects. The use of hydroxychloroquine is unlinked to a greater threat of infection or malignancy. Same goes to chloroquine. Gastrointestinal symptoms, including as nausea, vomiting, diarrhea, and abdominal pain, are the most prevalent side effects of these antimalarial medicines. In addition, some investigations have found hydroxychloroquine-mediated and/or chloroquine-mediated cardiotoxic effects, and hydroxychloroquine-associated myopathy including rhythm problems and cardiomyopathy progression in individuals with rheumatic illnesses. (Valentini & Zmerly, 2020). Antimalarial arrhythmia is more likely to occur in individuals who already have a cardiac rhythm abnormality, and the risk is dose-dependent. The maximum daily dose of hydroxychloroquine, according to ophthalmology standards, is 5 milligram per kg actual of body weight due to an increased risk of retinopathy (Valentini & Zmerly, 2020). A yearly ophthalmology examination is required. Originally used to treat RA, hydroxychloroquine has lately been discovered to be useful in treating of connectivities. The immunological system is affected by these drugs in a variety of ways. These medications elevate lysosomal pH, which inhibits the autophagy processes that enhance the inflammatory response, at the lysosomal level. Toll-like receptors (TLRs) function by attaching to the endosome and blocking RNA and DNA transcription, hence inhibiting the transcription & synthesis of pro-inflammatory cytokines(IL-6, TNF alfa, IL-1). $C_{18}H_{22}CIN_3$ & $C_{18}H_{22}CIN_3O$ bind to the virus's

glycoprotein E2 on its top, prohibiting it from interacting with the cell in COVID-19 infection. This activity might explain why the viral load has decreased. The PCR nose swabs testing were negative 100% all time in patients who took azithromycin (500 milligrams on the 1st day, then 250 milligrams daily for the following four days). (Valentini & Zmerly, 2020).

TABLE 1. Antirheumatic drugs applied in COVID-19 treatment based on the stages of the disease.

Stages of the Disease: COVID-19 can be divided into three distinct phases. (1) The initial phase is marked by fever, lethargy, dry cough, anosmia, taste changes, nasal congestion, and diarrhea, and is caused by a virus. These symptoms are usually minor and can mimic a viral infection similar to the flu. Initial lymphopenia was detected, as well as an elevation in C-reactive protein (CRP) and PT-INR; this is a typical IL-6 expression. The second phase is characterized by dyspnea and hypoxia in the lungs. (3) Respiratory distress syndrome (SARS) is the third phase, which can progress to a clinical presentation of vasculitis with embolism, DIC, septic shock, and metabolic acidosis.(Valentini & Zmerly, 2020). A distinct pathology distinguishes the three phases. The immunological response is similar to that of a viral respiratory syndrome in the initial phase; the mechanisms are similar to those of a flu syndrome.If the first phase does not resolve entirely, the clinical manifestation progresses to the second phase, also known as the respiratory phase, in which the patient develops dyspnea. Auscultation of the chest is not suggestive at this point, but there is a rapid and progressive fall in oxygen saturation. Even in patients with weak or limited respiratory

symptoms, lung CT images indicate interstitial pneumonia with typical "ground-glass opacity" and "consolidation" elements.(Valentini & Zmerly, 2020).

	Stage 1	Stage 2	Stage 3
Antimalarial	+	+	-
Monoclonal Antibodies	-	+	+
Corticosteroids	-	±	+
NSAIDs	-	±	±
Vitamin D	±	-	-
LMWH (Low Molecular Weight Heparin)	+	+	+

4.2. Monoclonal Antibodies

4.2.1

Tocilizumab

The fast and rapid development of the disease's second and third stages is marked by IL-2 and IL-6, and also γ interferon, BNP and d-dimer (Valentini & Zmerly, 2020). The cytokine storm is to blame for the progression of SARS-CoV-2 symptoms to a catastrophic DIC presentation. The concentrations of IL-10 in individuals who enter this critical condition are 10 times greater than in control patients. A hemophagocytic lymphohisticytosis (sHLH) is caused by a cytokin storm that begins in the 2nd stage of the illness and spreads fast in the 3rd stage, resulting in a organized hyerinflammation including various organs presenting that can lead to mortality (Valentini & Zmerly, 2020). Tocilizumab ® is a membrane-bound (mIL-6R). IgG1 recombinant monoclonal antibody directed against the soluble IL-6 receptor (sIL-6R). Guidelines of Italy support the use of tocilizumab (at a dose of eight milligram per kilogram, with a second dose after 1 hour and then a probable 3rd dose another 1 to 1.5 days) based on clinical response (Valentini & Zmerly, 2020). According to current statistics, 70% of patients treated with this medication had a good response. This medicine is not suggested if a person was already diagnosed with TB since it might lead to a relapse of TB and the development of a miliary diffusion aspect. (Valentini & Zmerly, 2020). Tocilizumab causes a quick drop in C-reactive protein, an IL-6 serological marker. Additionally, quick increases in blood oxygen pressure and dyspnea have been noted, along with a decrease in temperature. Tocilizumab is used to treat SARS-CoV-2 illness in phases 2 and 3 (Valentini & Zmerly, 2020).

4.2.2

Sarilumab

Sarilumab is an IL-6 receptor monoclonal antibody. For this continuing COVID-19 compound, an Italian pharma agency is conducting a research. Tocilizumab's rationale for usage is similar to that of tocilizumab (Valentini & Zmerly, 2020).

4.2.3

Anakinra

IL-1 is the first cytokine to increase during a hyperimmune inflammatory response, continued by IL-6 and Tumour Necrosis Factor α. As a result, IL-1 must control in the beginning in the immune response.

Anakinra is an IL-1 receptor antagonist made in Escherichia coli cells using recombinant DNA technology (Valentini & Zmerly, 2020). It has been utilized in the treatment of RA in the past and is currently being used in the treatment of auto inflammatory illnesses; it is administered regularly and subcutaneously (Valentini & Zmerly, 2020).

4.2.4

Canakinumab

Canakinumab is a monoclonal antibody that fights IL-1 beta in humans. It's now approved throughout Italy for treating refractory gouty arthritis, periodical autoinflammatory fever, and Still's illness. (Valentini & Zmerly, 2020).

4.2.5

Janus kinasi inhibitor

Tofacitinib, baricitinib are substances applied for treatment of refractory RA that work at the cell by influencing DNA transcription (Valentini & Zmerly, 2020). They limit the production of many pro-inflammatory cytokines by modifying the transcription of extracellular signals to the nucleus. One of the ways the virus travels up is by endocytosis (Valentini & Zmerly, 2020). ACE2 receptors, namely AT2 epithelial cells of alveolar, control this. The numb associated kinase (NAK) family, which includes AP2-associated protein kinase (AAK1) and another kinase dubbed GAK, is one of the endocytosis regulators (Valentini & Zmerly, 2020). Blocking these two kinases may prevent viral particle endocytosis and secondary assembly (Valentini & Zmerly, 2020).

4.3. Vitamin

Injecting of an adequate dose of D vitamin might use as part of a strategy to prevent and minimize risk factors for SARS-unfavorable CoV-2's development. Vitamin D has long been known for its immunomodulatory properties and antagonistic effect on viral proliferation in the respiratory system. Borella34 looked explored how vitamin D, the immune system, and infectious disorders interact, focusing on the link between respiratory and enteric infections and hypovitaminosis D. Vitamin D's potential to enhance catelicidine and beta-defensins with anti - viral and immunomodulatory properties has been linked to otitis media, Clostridium infections, vaginosis, urinary tract infections, sepsis, influenza, dengue fever, and hepatitis (Valentini & Zmerly,

2020). In a research done by Kim35, individuals with community-acquired acute pneumonia had lower levels of 25 (OH) D (14 8 ng/ml). The treatment of vitamin D3 (which is 500 U/day) to individuals with inflammatory bowel disease lowers the risk of upper respiration path infections by 2/3 when 25 (OH) D levels are less than 20 ng/ml. A concentration of 25 (OH) D > 38 ng/ml has been linked to a 50% cutting in the incidence of acute respiratory infections (Valentini & Zmerly, 2020).

According to Grant et al., vitamin D may play a function in coronavirus prevention and therapy. (Valentini & Zmerly, 2020). Vitamin D, according to the scientists, decreases the threat of lung infections in 3 ways:

• Strong connections with barrier by lung must be maintained.

• In patients with COVID-19 antimicrobial peptides were expressed at a higher level. such as catelicidine and betadefensins, peptides with antiviral action (Valentini & Zmerly, 2020).

• Immunoregulatory activity was stimulated, which might be linked to the possibility of a cytokine storm and pneumonia. (Valentini & Zmerly, 2020).

4.4. Miscellaneous

Nonsteroidal anti-inflammatory medicines

Application of NSAIDs during COVID-19 infection has generated heated debate. The earliest research that looked at the efficacy of ibuprofen found that it was linked to a greater incidence of electrolyte water changes and worsening pneumonia. Although, there are differing viewpoints on the previous idea, since platelet aggregation decrease may serve a protective function in preventing microthrombotic progression. The usage

of nonsteroidal anti-inflammatory drugs (NSAIDs) is still debatable in the scientific community (Valentini & Zmerly, 2020).

Corticosteroids

The use of corticosteroids with in therapy of COVID-19 induced virus pneumonia or ARDS is currently being disputed (Valentini & Zmerly, 2020).

Corticosteroids reduce all cytokine cascades by acting at NF-K beta transcription. It's important to remember that the mechanism of action of these medications changes depending on the therapeutic dose threshold. Prednisone has an immunosuppressive effect starting at 25 mg per day and increasing to greater doses. During viral infections, on the other hand, steroids are known to decrease the immunological response (Valentini & Zmerly, 2020). As a result, the possibility of receiving corticosteroid therapy, as well as the phases of illness in where to begin medication and the drugs associated with it should all be carefully evaluated. The medicine to be utilized, the dose, the timing, and the mode of delivery are all unknown and undergoing testing. The current advice is to use a light dose, with a low to moderate dosage (0.5 to 1 milligram per kilogram per day of $C_{22}H_{30}O_5$) for short (7-day) duration (Valentini & Zmerly, 2020).

Low-molecular-weight heparins

Hyper inflammation is produced in the latter stages of COVID-19, with potentially significant local and systemic effects. This disease is associated with a poor prognosis. Manifestations of arterial and venous vasculopathy, small vessel thrombosis, and progression to significant and sometimes permanent lung diseases (pulmonary

fibrosis) are seen at the level of the lungs (Valentini & Zmerly, 2020). Severe ARDS and, in certain circumstances, DIC are the last phases of this highly dangerous clinical feature. A change in PCR, ferritin, and pro-inflammatory cytokines was detected during this time. Increased coagulation indices, such as fragments of fibrin D-dimer breakdown, coagulation factor consumption, and thrombocytopenia, are also seen (Valentini & Zmerly, 2020).

Chapter 5

Risk and evaluation of disease with drug and drug interactions in COVID-19

COVID-19 is labeled a global pandemic in 2020. Its fatalityrates are rapidly increasing because to a lack of treatment options. The SARC-CoV-2 sparked the outbreak continues expanding (Kumar & Trivedi, 2021). In the pathophysiology of this condition, the patient's immune response is crucial. In extreme cases, the mediators of this inflammatory factor were shown to reach the cytokine at maximum amounts. Due to alterations in drug pharmacokinetics, a hyper inflammatory state can produce severe anomalies in transporters and drug metabolic machinery, resulting in unforeseen therapeutic responses. The present state considers the necessity for therapeutic alternatives to alleviate and conquer the epidemic. Although COVID-19's slow development, no drug has been approved to have a significant impact on COVID-19 patient's therapy with no side effects. Despite not knowing about probable drug-drug interactions, the Food and Drug Administration has authorized a number of antiviral and anti-inflammatory medications to treat COVID-19 patients based on the data (DDI). Molnupiravir, favipiravir, and remdesivir, and are the most promising antiviral medications for developing the health of affected patients. Dexamethasone, a 1st steroid reported to have cured critically sick people. There have also been certain proteins with oligopeptides employed. The present study focuses on pharmacological modifications for COVID-19 sufferers with inflammatory diseases, as well as interactions with drugs transporter and enzymes that do drug-metabolizing (Kumar & Trivedi, 2021). The study provides a perspective on the potential for DDI to allow for

the personalization of these medications, hence improving their safety and efficacy. (Kumar & Trivedi, 2021).

5.1. Drug transporter pathways change in response to inflammation.

Inflammation is related to a variety of cytokine responses. The immunological processes homeostasis is maintained by this vast class of tiny cell-signaling proteins. The proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF-) are the main mediators of acute immune responses. These regionally generated cytokines may travel circulating and have a widespread impact via engaging to cell membrane receptor, parenchymal cell, vascular endothelium transporter and in a variety of organ during infection. Inflammation and immunological responses have a role in many acute and chronic disorders, affecting medication clearance by modifying the mechanism of drug transporters and the activity of drug-metabolizing enzymes (Kumar & Trivedi, 2021).

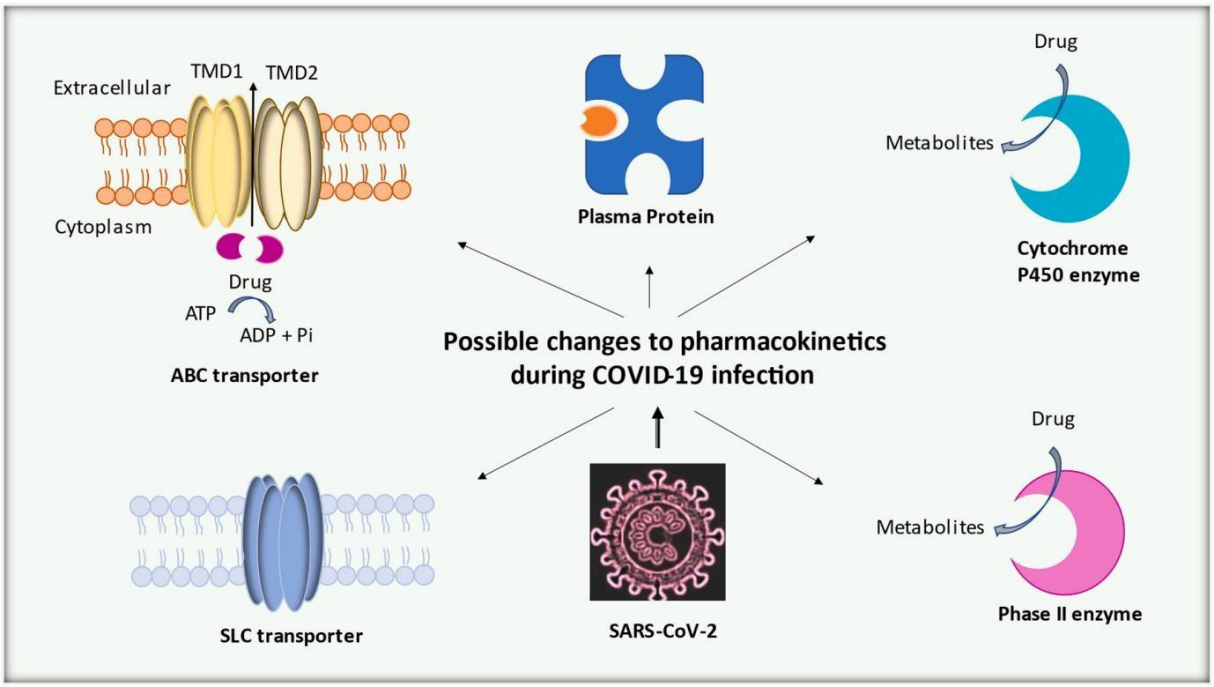

Figure 2: *Changes in the expression of important transporters and drugs metabolizing enzymes (Cytochrome P450 and Phase II) drove by the initial*

inflammatory reaction in COVID-19 influence in changing drug distribution and pharmacokinetics (Kumar & Trivedi, 2021).

In terms of inflammatory response, Pgp is among the widely researched ABC transporters in terms of inflammatory response. IL-6 has been associated to Pgp messenger RNA and protein presentation in hepatic cells line and on mice on vivo, according to multiple studies (Kumar & Trivedi, 2021). In inflammatory settings, the intestinal epithelium in humans revealed a reduction in Pgp expression. Caco-2 is a cell line from human enterocytes, was treated with TNF used as a universal model for permeability experiments, led in a reduction in Pgp expression and activity (Kumar & Trivedi, 2021). Second, BCRP (breast cancer resistance protein), the most extensively researched ABC transporter, has been examined. In the recent past primary human hepatocytes, BCRP activity and expression were reduced after treatment with IL-6, similar to Pgp, but TNF- α therapy resulted in BCRP increase (Kumar & Trivedi, 2021). IFN gamma effect on hepatocyte of humans resulted in a considerable reduction in BCRP mRNA expression. After treatment with IL-β1, IL-6, and TNF-α, the expression and activity of BCRP in a human brain cell line decreased significantly. Proinflammatory cytokines are also thought to be important MRP2 mediators. Recently, it was shown that Interleukin-β1, Interleukin-6, and Tumour necrosis factor-α all significantly reduce MRP2 mRNA and protein expression in human and rat hepatic cell lines (Kumar & Trivedi, 2021). Overall, the acute inflammatory response modulates the expression of MRP2, BCRP, Pgp and numerous other important transporters; one research on patients with inflammatory bowel disease (IBD) discovered the influence of inflammation on SLC transporters. SLC transporter

mRNA levels were dysregulated in IBD patients (ENT1, ENT2, CNt2, OATP2B1, and OATP4A1), which is linked to tissue inflammation and provides evidence of inflammation signal in the control of solute carrier expression. During inflammation, several transcription factors are active, and they have a vital duty in controlling of drug transporters & metabolizing enzymes. (Kumar & Trivedi, 2021). Several great studies on the molecular mechanisms of transporter modulation during inflammation have been published elsewhere (Kumar & Trivedi, 2021).

5.2. Inflammation causing changes in the activity of drug metabolizing enzymes.

Most medications' metabolic biotransformation includes CYPs, which are the key contributors. Regulation of CYPs, like drug transporters, has been linked to inflammation in a variety of infectious and metabolic illnesses, including virus infection (Kumar & Trivedi, 2021). The most common cause of inflammation is changes in hepatic Cytochrome P-450 is a cytokines produced for inflammatory response process. Multiple cytokines have been observed to have a role in the regulation of one enzyme, although single cytokine may control sublcesses of enzymes. Because medication pharmacokinetics will be varied based on type of illness and released cytokines, including the administered, control is critical when considering drug interactions (Kumar & Trivedi, 2021). CYPs activity has been altered by cytokines in a variety of animals, including humans, employing hepatocytes including in vivo in rats, mice and people. Extrahepatic CYP was similarly inhibited by inflammatory mediators. IL-1, IL-6, TNF-, and IFN- are the most common proinflammatory cytokines that inhibit expression and activity of CYP. All other cytokines, such as IL-2 and IL-10, had a similar impact.

The principal inflammatory agent that has been discovered as having a considerable inhibitory affect during activities of many CYPs is IL-6. In rat hepatocytes, human recombinant IL-6 inhibited phenobarbital-mediated activation CYP2B1/2 in a concentration-dependent manner. It lowered the activity of several CYPs to varying degrees. In distinct human hepatoma cell lines, human recombinant IL-6 therapy significantly reduced mRNA levels of CYP1A1, CYP1A2, and CYP3A3. In rats, chronic inflammatory responses generated by turpentine or bacterial lipopolysaccharide suppressed hepatic CYP1A2, CYP2A5, CYP2C1, and CYP3A11 (Kumar & Trivedi, 2021). IL-6's effect on CYPs induced by cancer has been studied in a number of studies. The use of monoclonal antibodies for Interleukin 6 or the Interleukin 6 receptor to counteract these effects has established the relevance of Interleukin 6 in malignancy-mediate inhiditation of CYP3A (hepatic) (Kumar & Trivedi, 2021).Anti-IL-6 antibody infiltration in initial humans hepatocyte treated with Interleukin was also examined. Anti-IL-6 antibody infiltration in initial human hepatocytes treated with InterleukinL 6 was also examined. Interleukin 6 also efficient in inhibiting omeprazole and rifampicin from inducing CYP1A2 and CYP3A4, respectively.

The role of cytokines in inhibiting CYP activity is not well understood. A decrease in CYPs mRNA, on the other hand, is assumed to indicate a transcriptional process affecting a number of transcriptional factors. (Kumar & Trivedi, 2021). Pyrolidine dithiocarbamate, for example, is an NF-kB inhibitor that can prevent the inflammatory drop in CYP1A2 activity. Many genes are addressed by the Pregnane X Receptor (PXR), the most prominent of which being CYP3A4. PXR is controlled by NF-kB

factors, which are regulated by inflammatory stimuli, resulting in hepatic CYP expression modification. The showing of glucocorticoid receptors and constitutive androsterone receptors was lowered when NF-kB was activated (CAR). It has something to do with the CYP genes. In COVID-19 patients' peripheral blood, proinflammatory cytokines were shown to be increased (Kumar & Trivedi, 2021). Because regarded as critical interval in the way and that its growth is related to a weak prediction The most significant focus for anti-cytokine treatment has been identified as IL-6. It is generally established that changes in a transporter's expression, as well as the activity of DMEs, may affect a drug's PK/PD; as a result, interindividual variations in medication effectiveness and hazard may necessitate the use of prescription medications in inflammatory response. (Kumar & Trivedi, 2021). Drug interactions are more likely when many medications are taken at the same time (Kumar & Trivedi, 2021).

5.3. COVID-19 treatment agents

Remdesivir

Remdesivir is an analog of the adenosine triphosphate. It was created to combat Ebola and Coronavirus. Remdesivir inhibits the viral replication enzyme RNA dependent RNA Polymerase, which is required for viral replication. By avoiding exoribonuclease's proofreading function, it promotes the early end of viral transcription. Remdesivir is effective against a wide range of viruses, including SARS-CoV and MERS-CoV. Data on clinical pharmacokinetics is still a mystery. Furthermore, human safety data is available on the internet. Remdesivir has already proven that it can suppress human and Zoonotic CoV at sub-micro molar

concentrations in tissue culture tests. MERS-CoV infected nonhuman primates showed similar effectiveness (rhesus monkey). It has paved the way for the development of a possible COVID-19 therapy. According to updated statistics, COVID-19 hospitalized patients, Remdesivir had little or no impact, as measured by total fatalility, ventilation start with time in medical (Kumar & Trivedi, 2021). The combination of Remdesivir and baricitinib has showed positivity for recovering of COVID-19. The co-medication treatment was more effective than Remdesivir alone in reducing recovery time and speeding up clinical improvement (Kumar & Trivedi, 2021). There has been evidence that this combination has less significant side effects. When CQ or HCQ is used with Remdesivir, the antiviral activity of Remdesivir may be reduced. Despite rapid clinical improvement, Remdesivir and bericitinib in another combo, a CYP3A4 substrate, resulted in significant adverse effects (Kumar & Trivedi, 2021).

5.3.1.

Drug and Drug interaction

Remdesivir's PK profile is linear. The GS-441524 had a half of 24 hours, but Remdesivir exhibited no significant change in half-life in healthy people. According to original statistics from healthy people, Remdesivir is substantially metabolism by CYP3A4, CYP2D6 and CYP2C8. Although no clinical investigations on Remdesivir's DDI have been conducted, mathematical predictions of DDI liability have been made using current phase 1 and data of in-vitro. Due to the high to moderate extraction ratio, the consequence of indicer on Remdesivir's PK would be considerably decreased if Remdesivir had a low hepatic ratio of extracting (0.60 0.80) and IV route

of administration (Kumar & Trivedi, 2021). The stimulation of CYP3A by the potent inducer rifampicin is expected to reduce Remdesivir exposure by up to 30%. Similarly, total CYP3A inhibition would be expected to raise Remdesivir levels by 4%, compared to a 20-fold increase in midazolam exposure. A physiologically based pharmacokinetic model (PBPK) that captures the invitro inhibition efficacy and in vivo PK of Remdesivir was constructed using the SimCYP software Evaluate Remdesivir's ability to block DMEs and transporter in vivo (Kumar & Trivedi, 2021).

The change in pravastatin (OATP), midazolam metformin (MATE1), pravastatin (OATP), rosuvastatin (OATP/BCRP), midazolam (CYP3A), and pravastatin (OATP) research vulnerability was forecasted using (AUC) BCRP, CYP3A, OATP1B3, and MATE1 unbound inhibition constants in vitro. The time of Remdesivir delivery relative to the prob drug was tuned for these PBPK simulations to predict the greatest DDI, which was crudely tied to the administration of Remdesivir, as a result, the infusion came to a halt when the probe detected the highest plasma concentration (Kumar & Trivedi, 2021). At therapeutic Remdesivir doses with COVID-19, simultaneously administering of Remdesivir is estimated to enhance probing drug AUC transporter. Prior studies showed that 200 milligram loading dosage and then 100 mg maintenance doses in about 5–10 days was effective in treating COVID-19 (Kumar & Trivedi, 2021).

5.3.2. Disease and Drug interaction

In vitro evidence suggests inflammation lowers the mRNA expression for various isoenzymes CYP450 and transporters, such as CYP3A4, CYP2D6, CYP2C19,

CYPC9, CYP2B6 and CYP1A2. As a result, inflammation may have an impact on their pharmacokinetics (Kumar & Trivedi, 2021).

5.4. Azithromycin

In vitro testing demonstrated that azithromycin (Pfizer, NY, USA) is effective against Ebola. Furthermore, azithromycin is thought to be capable of preventing severe respiratory tract infection (Kumar & Trivedi, 2021). The antibiotic azithromycin is absorbed by a number of tissues, including the lungs. In conjunction with HCQ, COVID-19 patients were treated with azithromycin. (Kumar & Trivedi, 2021).

Drug and drug interaction

Azithromycin is macrolide antibiotic that is applied to prevent secondary infections when combined with COVID-19. It has a strong affinity for tissue and is widely distributed throughout the body. In the body, it has a half-life of two to four days. Azithromycin that has been proven to boost serum levels when paired with a P-gp substrate (such as Digoxin). It also inhibits CYP3A4, OATP1A2, and OATP2B1. COVID-19 and HCQ in combination have been shown to minimize COVID-19 related mortality. Pharmacodynamics, not pharmacokinetics, is the dangers of possible interactions. The influence on QT prolongation was established while giving azithromycin as a co-medication. When azithromycin was combined with HCQ, the QT interval lengthened highering the threat of heart attack and cardiovascular fatality (Kumar & Trivedi, 2021).

Chapter 6

Pathophysiological processes, immunopathology, and treatment choices

Despite the global deployment of preventative steps to battle COVID-19, which is occurs due to SARS-CoV-2, continues to spread internationally (Eijk et al., 2021). Although most of COVID-19 cases have little, self-limiting course, a very small group of people develop a more serious illness, ranging from pneumonia to ARDSs to various organ dysfunction. The advancement of COVID-19 is assumed as the consequence of a complex interaction between a number of pathologic processes, which are all thought to have a role in orchestrating COVID-19 infection and leading to particular tissue and organ death. In this context, dissecting current information of COVID-19 immunopathogenesis is crucial not to increase understanding pathophysiology, but to support the justification for both innovative and recycled treatment approaches (Eijk et al., 2021). During the infection various immune mediated mechanisms relating to basic immunology, adoptive immune response, and autoimmune are important. Pathology results in COVID-19 sufferers' tissues samples provide critical information for understanding pathophysiology and devising evidence-based treatment regimes. (Eijk et al., 2021). This article gives updated description of the major pathological abnormalities seen during COVID-19 in the most often afflicted organ systems, with a focus on immunopathology. Supportive therapy with the application of repurposing or symptomatic medications like Remdesivir, dexamethasone and anticoagulants are among the current COVID-19

therapeutic methods. In the end, the most efficient way to tackle COVID-19 is to prevent it from spreading, which necessitates the development and application of effective vaccinations (Eijk et al., 2021).

6.1. Immune defects and Immunopathology

Natural immunity response

In the case of the infection, the natural immunity is the first line of defense. SARSCoV-2, like SARS-CoV, can be aided in cell entrance by furin and neuropilin. Infected cells that release enough IFN generate an antiviral immunological state that inhibits virus multiplication and promotes cell death in the host to save it from virus multiplication. Multiple Severe acute respiratory syndrome 2 proteins has discovered to suppress the production and signaling of antiviral type I interferon (IFN-I) (Eijk et al., 2021).

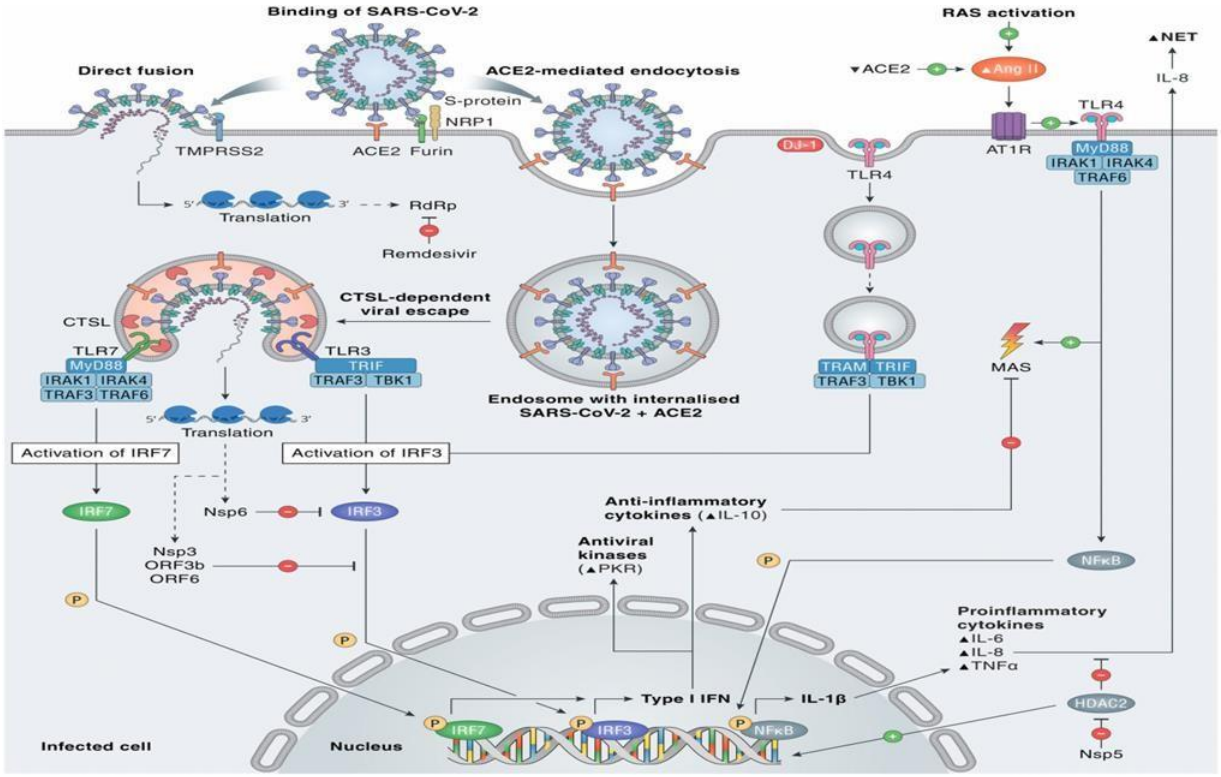

Figure 3: *Entry of SARS-CoV-2 and immunological activation* (Eijk et al., 2021).

The delayed type-I interferons reactions are accompanied through unfettered replication of virus and dispersal throughout infection site, leading to an increase in type-I interferons, which has exacerbate hyper inflammatory as disease advances seriously (Eijk et al., 2021). Infection of SARS-CoV-2 produced extraordinarily low levels of IFN despite eliciting a powerful pro-inflammatory cytokine response, according to transcriptome analysis of respiratory cell types. There's a considerable upregulation of neutrophil chemoattractants and monocyte in this investigation, which is consistent with the regularly seen macrophage and polymorphonuclear leukocyte infiltration of the lungs in autopsied COVID-19 patients (Eijk et al., 2021). Individual differences in IFN responses, like in other viral infections, may help for variety clinical symptoms in corona. Two paired found various underlying IFN-I signaling flaws in life-threatening COVID-19, including inborn mistakes of TLR3-

and IRF7-dependent IFN-I immunity, as well as the presence of IFN-I neutralizing autoantibodies. The latter research found that neutralizing autoantibodies against IFN-I were present in 10.2% of 987 patients with life-threatening COVID-19 pneumonia, which was 15-fold greater than the general population, and that males were more likely to have them (Eijk et al., 2021). These findings support the use of IFN-based therapies for COVID-19 in the early stages, when only minor symptoms are evident (Eijk et al., 2021).

6.2. COVID-19 pathophysiological mechanisms that have been proposed

COVID-19 spread as a result of a complex interaction of numerous physiological and pathological processes, which include specific cytotopathic impacts of SARS-CoV-2, ACE2 dysregulation RAAS disbalance and decreased inactivation of des-Arg9-bradykinin; (3) a dysfunctional immunologic reaction depicting a 'storm of cytokine; Immunopathology may be a distinguishing hallmark of severe disease, but the proportionate contributions and interaction of such related processes to COVID-19 related organ failure are unclear.(Eijk et al., 2021).

6.3. Adaptive immune response

By activating cytotoxic T-cells, which kill infected cells, and B-cells, which create neutralizing antibody targeting specific-virus antigen, the adapted immunity systems performs a critical part for SARS. The adaptive immune system plays a big role in SARS-CoV-2 clearance (Eijk et al., 2021). COVID-19 causes blood lymphopaenia, which is marked by a reduction in and B-cells, CD8+ T-cells and CD4+ T-cells. Due to the crucial involvement with in assembling the virus elements on antigens presentation as well as subsequent activation of adoptive defense,

lympopenia might also described in part with an aberrant natural immunological reaction with reduced IFN-I levels. COVID-19-associated lymphopaenia can be caused by T-cell infection with SARS-CoV-2, cytokine-induced lymphocyte apoptosis and pyroptosis, lymphocyte sequestering as in respiratory system or any other organ, MAS-related haemophagocytosis, damaging viral-inducing tissue f lymphatic organs, and impaired bone marrow haematopoiesis of lymphatic organs. SARS-CoV-2 was identified in the spleen and lymph nodes, as well as with pathological alterations, indicating the straight SARS-CoV-2 cytotoxicity in lymphatic organs might obstruct COVID-19 adaptive immune response. Loosing germinal center production both in the lymph nodes and spleen might explain why some people have poor humoral immunity, putting them at risk of reinfection (Eijk et al., 2021). Despite this, the vast majority of COVID-19 patients with mild-to-moderate disease develop a robust adaptive immune response involving T-cells (against S-protein- and nucleoprotein/membrane protein-derived antigens) and neutralizing antibodies (against S-protein-derived antigens) that lasts for months after primary infection (Eijk et al., 2021).

Chapter 7

Potential therapies for COVID-19

COVID-19 has no FDA-approved treatment in present time; nonetheless, maximum efforts and research continue and are continuing, respectively. As Kupferschmidt et al. have pointed out; using a SARS-CoV-2-accurate way to development of drugs makes sense. Although figures of the present figure for scheduled and current clinical trials differ, it is possible that there may exist many as 800 worldwide (Becker, 2020). The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) on March 28, 2020, allowing the addition of chloroquine phosphate (medical grade) and hydroxychloroquine sulfate to the strategic national stockpile (SNS) (Becker, 2020). Companies were expected to raise production for the commercial market as well, to prevent shortages for autoimmune disease patients who rely on hydroxychloroquine sulfate (Plaquenil®) for routine therapy (Becker, 2020). The HHS Office of the Assistant Secretaries for Preparedness and Responses oversees coordinated use of chloroquine phosphate and hydroxychloroquine sulfate (ASPR).

Responding, the APSR's BARDA NIH and the Food and Drug Administration to ensure that patients and prescribers should have access to statistics outlining critical details regarding these medications and how to administer them, including probable risk and interactions of drugs (Becker, 2020).

7.1. Chloroquine and its effects in COVID-19

Hans Andersag, a chemist working for Bayer AGTM on chemicals having anti-malarial effects, developed chloroquine in the early 1930s. It's a 4-aminoquinoline chemical that's consumed through mouth which have lengthy history of mass administration for plasmodium vivax, plasmodium ovale, and plasmodium malariae prophylaxis (Becker, 2020). Due to well-documented resistance, it is rarely used to treat plasmodium falciparum. Chloroquine is rapidly absorbed and has a large volume of distribution. It is metabolized in the liver and produces the major metabolite desethylchloroquine. In the urine, approximately half of the medication is eliminated unaltered (Becker, 2020).

Action Mechanisms

Chloroquine accumulates in lysosomes, in which it alters the pH of the cell and is retained in a protonated state. Chloroquine's potential for elevating lysosomal and endosomal pH, which restricts the right of virus to remove genomic material of the cell and proliferate, is assumed to be responsible for the antiviral action. It also restricts RNA dependent polymerases, inhibits glycosylation of envelope glycoproteins, and reduces endosomal discharge of iron required for DNA replication and functions as a zinc ionophore, increasing internal zinc content and restricting

essential post-translational stages in freshly created protein (Becker, 2020). The antithrombotic effects of chloroquine have piqued people's curiosity. Despite the fact that its contribution to total benefit may be minimal and uncertain in patients with COVID-19, chloroquine reduces neutrophil extracellular trap production, platelet activation, and circulation tissue factor in mice. (Becker, 2020).

Cardiovascular Effects

Chloroquine variably changes coronary arterial vasodilation in mice which is diabetic. It reduces the creation of nitric oxide in human coronary artery endothelial cells. (Becker, 2020). In individuals with coronary artery disease, the potential clinical impact is uncertain. Chloroquine has been proven to suppress autophagy in animal studies, leading in improved diastolic function in diabetic mice. Beneficial mechanisms include auto phagolysosomes that have died apoptosis, and heart fibrosis (Becker, 2020).

Potential risks

Chloroquine treatment at high dosages has been linked to cardiovascular effects such as vasodilation, hypotension, reduced myocardial function, and arrhythmias (reviewed in Ben-Zvi). Several organizations have reviewed the possible cardio toxic effects of chloroquine. Glucose absorption, in vivo cardiac function, ex vivo cardiac function and mitochondrial function were all studied by Blignaut and colleagues. (Becker, 2020). The trials utilized obese male Wister rats that were given different doses of

chloroquine When dosages of 10uM or greater were used, heart function was impaired. Ex vivo exposure showed no effect on mitochondrial function, although it did diminish cardiac output over time. The Centers for Disease Control and Prevention published an online warning about non-medicinal chloroquine phosphate items with also the dangers they pose to people upon ingestion, including fatality (Becker, 2020). It's also important to remember and be aware of the risks of using medical hydroxychloroquine and chloroquine at greater doses. Q-Tc prolonging can produce cardiac arrhythmias, such as torsades de pointe and ventricular tachycardia, as well as hypokalemia (Becker, 2020). Atrioventricular & Bundle branch block are two more electrocardiographic effects. Non-cardiovascular side effects include diarrhea, vomiting, and nausea as well as aplastic anemia, thrombocytopenia, convulsions, shock, death and coma (Becker, 2020).

7.2. Hydroxychloroquine and its effects in COVID-19

Using SARS-CoV-2 infected Vero cells, Yao and colleagues assessed the pharmacological action of hydroxychloroquine. Integrating in vitro data was used to create pharmacokinetic models. The amounts of hydroxychloroquine in the lung fluid were simulated. It was discovered that hydroxychloroquine (EC50=0.72 M) is more powerful than chloroquine (EC50=5.47 M). A loading dose of 400 milligramg two times a day of hydroxychloroquine sulfate delivered orally for the infection, followed by a maintain dose of 200 milligrams multiple times 4 days, may be recommended. In VeroE6 cells, the in vitro cytotoxicity of hydroxychloroquine was measured, and the 50 percent cytotoxic concentration (CC50) for HCQ was found to be 249.50 M. At four different infection multiplicities (MOIs), the dose–response relationship was

determined by counting viral RNA copy numbers in the cell supernatant 48 hours after infection (Becker, 2020). At each of the MOIs, the 50 percent maximum active concentrations (EC50) of hydroxychloroquine was 4.51, 4.06, 17.31, and 12.96 M. (0.01, 0.02, 0.2, and 0.8). Over the course of two weeks, Gautret and colleagues conducted an open-label, single-arm clinical trial. A total of 20 COVID-19 verified people receiving 600 mg of hydrochloroquine daily (8 lower respiratory tract symptoms, 6 asymptomatic, and 22 upper respiratory tract symptoms). (Becker, 2020).

According to the medical literature, treated patients had lower viral load carriage by day 6 than untreated individuals. The effects of hydroxychloroquine were amplified when azithromycin was added (Becker, 2020)

7.3 Remdesivir:

A Review of Its Research and Development Resulting to COVID-19 Urgent Use Approval for treating COVID-19

Remdesivir (GS-5734) was developed by Gilead Sciences in collaboration with the CDC and the US Army Medical Research Institute of Infectious Diseases (USAMRIID). They wanted to find treatment drugs for RNA-based viruses with worldwide pandemic potential, such as EBOV and the Coronaviridae family viruses that caused Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which were discovered after the program, began (SARS). (Eastman et al., 2020)

Based on past knowledge of potent antiviral drugs targeting RNA viruses, a library of 1000 small molecules centered on nucleoside analogues was assembled as a starting point for discovery (Eastman et al., 2020Because nucleosides is very slightly soluble to cells (hence has poor strike rating in cellular screen such as antivirus screenings), altered nucleoside prodrugs such as monophosphate, ester, and phosphoramidate prodrugs make up a significant portion of the library. This drug is usually porous, is metabolized within cell for liberating nucleosides or phosphorylation nucleosides. (Eastman et al., 2020). The cytoprotection effect (CPE) assay was used to determine antiviral activity. A live virus was cultivated using such a targeted cellular lines, with effectiveness of a testing agent to stop cell death was assessed using a conventional viability assay (Eastman et al., 2020). In a 2012 study, it was shown to have CPE action against SARS strain Toronto 2 (IC50 = 2.2 M) by not causing cytotoxicity in the CPE assay's host Vero African green monkey kidney epithelial cells.(Eastman et al., 2020). Remdesivir suppressed EBOV replication in HeLa cells with an IC50 of less than 100 nM, according to Madelain et al. and that it sustained effectiveness in vivo nonhuman monkey EBOV infection models, but GS 441524 was ineffective. Warren et al. discovered that, in addition to EBOV, With an IC50 of 340 nM in vitro, Remdesivir exhibits antiviral exercise against a variety of different virus, such as the coronavirus MERS. (Eastman et al., 2020).

Various researchers examined Antiviral Effectiveness in vitro and in vivo after demonstrating that Remdesivir has wide action against viruses RNA, supporting its activity against coronaviruses. SARS and MERS zoonotic coronaviruses, as well as the circulating human coronaviruses HCoV-OC43 and HCoV-229E, which cause the

common cold, were found to have antiviral activity (Eastman et al., 2020). Further, in a nonhuman monkey in vivo model, remdesivir was proven to be beneficial in both preventing and treating MERS, according to de Wit et al. The European Medicines Agency produced compassionate use literature that detailed the pharmacokinetics of Remdesivir. The prodrug had a brief plasma ½ life (t1/2= 0.39 h) but long-term internal cellular level of triphosphate version after daily treatment of nonhuman primates with 10 mg per kilogram. Remdesivir has been shown to be effective against SARS-CoV-2 and other coronaviruses in vitro and in early in vivo animal models (Eastman et al., 2020).

To investigate antiviral activity against SARS-CoV-2 Remdesivir employed qRT-PCR to measure virus replica numbers in contaminated Vero E6 cells. In this study, the IC50 was 770 nM, while the IC90 was 1,760 nM (with cytotoxic levels >100 mM). de Wit et al and Sheahan et al also established Remdesivir's in vivo efficacy over similar coronaviruses in decreasing viral replication and reducing viral-associated diseases. (Eastman et al., 2020). These results, combined to safety profile of Remdesivir's in the EBOV medical trial, support further research into Remdesivir as a potential treatment medicine for adaptability in the SARS-CoV-2 pandemic. In 2014, Gilead Sciences began medical trial of Remdesivir for EBOV, motivated by the EBOV epidemic and based on in vitro and animal models in vivo efficacy against the EBOV. Gilead applied for FDA clearance under the animal rule of FDA, which enables the use of animal efficacy data for drugs at which human testing are neither practicable nor acceptable (Eastman et al., 2020).

Chapter 8

Limitation & Future Recommendation

Limitation:

Though there is many active drugs available for the treatment of COVID-19 disease, there's aways some boundaries and limitations for the dosage and the drugs. If we talk about remdesivir, Remdesivir is a nucleoside monophosphoramidate prodrug that was licensed by the FDA in 2019 to treat coronavirus infection (COVID-19). However, the clinical efficacy of remdesivir for COVID-19 is debatable, as multiple studies have demonstrated no statistically significant differences in time to clinical improvement or death between the remdesivir-treated and control groups (Eastman et al., 2020). Similarly, remdesivir's inability to provide a clinically significant advantage over other investigational treatments in Ebola patients contrasts with excellent, curative preclinical evidence in rhesus macaque models. Many people have been perplexed by the considerable discrepancy between the impressive preclinical evidence and remdesivir's poor clinical effectiveness in both COVID-19 and Ebola (Eastman et al., 2020).

Future Recommendation:

- In order to determine the relative risk of infection, the incidence of SARS-CoV-2 infection should be tracked over time in large groups of people with and without cancer, using probabilistic sampling methods.
- To quantify mortality risk, both in-hospital and community deaths must be considered; cause of death data can be linked to COVID-19 monitoring data for this purpose.
- Enhance public health and health-protection efforts & Create a global emergency response system that is self-contained.
- Strengthen ties with multi-sector emergency response structures.
- Expand prevention and preparedness research.
- Leadership that is both courageous and collaborative.
- Restore the enviroment's greenness.

Chapter 9

Conclusion

The COVID-19 epidemic had devastating health and economic implications throughout the world. Despite the fact that several treatments have been proposed, there are currently no particular alternatives for treating COVID-19. Strict quarantine measures for the general population appear to be the only strategy now viable and proved to reduce the infection rateThe best effective proven treating approach, as well as specifically planned randomized clinical studies, are urgently needed to curb the development of COVID-19 and avoid the consequence of anther subsequent pandemic (Pascarella et al., 2020).

Our literature analysis demonstrates the importance of antirheumatic drugs and their therapeutic potential; nevertheless, there is a dearth of clinical data to support their use, and more randomized controlled trials are needed. The present problem is to distribute the existing medications in the best possible combinations and at the right moment throughout the disease's progression (Valentini & Zmerly, 2020).

The current evaluation highlighted the possibility of a medication interaction risk with the specified medicine in the treating of COVID-19. ABC and SLC transporter, on the other hand, are well-known for their function in disposition of primarily antivirul medicines and their ability to participate in a variety of drug interactions. Significantly, role of CYPs in COVID-19 infection medication and drug-drug interactions has been extensively studied, however certain medicines remain unclear.

As a result, inflammatory reactions have critical duty in or drug with drug combination or disease-drug in COVID-19 patients. (Kumar & Trivedi, 2021).

The immunopathological reaction to SARS-CoV-2 disease, which comprises downregulated acute and adapted defense as well as autoimmune, is critical factor in defining illness progression (Eijk et al., 2021). COVID-19 multifaceted pathophysiology, as well as its multiple illness phases, offer a foundation for a wide range of therapy prophylaxis, ranging from antiviral drugs sooner in the disease when gentle problems occur to antioxidant, immunomodulating, and antithrombotic therapy in more advanced disease (Eijk et al., 2021). A multilayer approach addressing several elements of physiological processes is needed to battle the COVID-19 (Eijk et al., 2021).

COVID-19 has no FDA-approved treatment in present time; nonetheless, maximum efforts and research continue and are continuing, respectively. As Kupferschmidt et al. have pointed out; using a SARS-CoV-2-accurate way to development of drugs makes sense. Although figures of the present figure for scheduled and current clinical trials differ, it is possible that there may exist many as 800 worldwide (Becker, 2020)

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