CHAPTER 1

COVID-19: PATHOGENESIS, EPIDEMIOLOGY, CLINICAL FINDINGS & TREATMENT

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PATHOGENESIS

In order to better understand the pathogenesis of COVID-19 disease, it is necessary to know the structure of the SARS-CoV-2 virus. As a result of SARS-CoV-2 replication, non-structural proteins (NSP), structural proteins and other accessory proteins are encoded. The most important structural proteins are spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins.

Each monomer of the S protein, which has a trimeric structure, is approximately 180 kDa and consists of two subunits. As a result of folding the S1 subunit onto itself, independent N-terminal domains (NTD) and C-terminal domains are formed. The N-terminal domain (NTD) and C-terminal domains are involved in the binding of the virus to the receptor on the host cell surface. The S2 subunit mediates the fusion and entry of the virus into the cell. Previously, it has been shown that inhibitory peptides prepared specifically for the S2 subunit domains for SARS-CoV and MERS-CoV infections inhibit the entry of viruses into lung cells.Although these inhibitory peptides are not at

the same level, it has been reported that they may be effective in SARS-CoV-2 infections. The S protein binds to the angiotensin converting enzyme (ACE2) receptor of the host cell, and this complex is subjected to a proteolytic process by the host type II transmembrane serine protease (TMPRSS-2), and the virus enters the cell. ACE2, which is especially expressed in type 2 alveolar epithelial cells, is accepted as the cellular entry receptor of SARS-CoV-2 to humans. Electron microscopy studies have shown that SARS-CoV-2 binds to ACE2 receptors with higher affinity than SARS-CoV. It has been reported that SARS-CoV-2 can enter cells independently of ACE2 in case of high viral load. The D614G mutation detected in the SARS-CoV-2 spike protein occurs in cases identified after April and May 2020 in the COVID-19 outbreak. In this mutation detected at residue 614 of the S protein, glycine replacement occurs instead of aspartic acid. In the SARS-CoV-2 genome, it has been detected in spike mutations accompanied by D614G mutation. It has been found that especially the D614G mutation is critical for infectivity and the presence of this mutation correlates with the high viral load in the nasopharynx of COVID-19 patients. After the SARS-CoV-2 host membrane fusion is achieved, the entry of the virus into the cell is completed and viral genomic RNA is released in the cytoplasm and converted into viral polymerase proteins. Uncoated RNA synthesizes 2 polyproteins (viral replicase polyproteins), pp1a and pp1ab, which encode NSP and form a replication transcription complex (RTC) in the double-membrane vesicle. RTC continuously duplicates and synthesizes a series of subgenomic RNAs that encode helper and structural proteins. Negative (-) polarity genomic RNA is synthesized and used as a template to create subgenomic or genomic positive (+) polarity RNA. While viral RNA and N structural protein are replicated, transcribed or synthesized in the cytoplasm, the S, M, and E protein are transcribed in the endoplasmic reticulum (ER) and transferred to the Golgi. Viral RNA - N complex, S, M and E proteins are assembled in the ER-Golgi spacer (ERGIC) to form a mature virion. This assembled structure is then released from the host cells to the extracellular space by exocytosis. Envelope membrane (E) proteins are relatively small viral structural proteins that assist in the assembly and release of virions. M proteins are 222 amino acid long structural proteins that function together with the E, N and S proteins and play an important role in RNA packaging. Nucleocapsid proteins (N), on the other hand, play an important role in the packaging of viral RNA into the ribonucleocapsid and assist in increasing viral RNA transcription and replication. It contributes to the establishment of order by interacting with the M protein during viral assembly. In

addition to structural proteins, the SARS-CoV-2 genome encodes a large number of NSPs that are involved in the replication and assembly stages of the virus. These proteins contribute to viral pathogenesis by preventing or modifying early transcription regulation, helicase activity, immunomodulation, gene transactivation, and antiviral response.

COVID-19 is a viral respiratory infection. SARS-CoV-2 that causes COVID-19 is a cytopathic virus; It particularly affects the bronchial epithelial cells and causes destruction of the infected cells within 3-5 days through apoptosis. Debris formed by the destruction of the bronchial epithelium and the viral particles released cannot be thrown out because the muco-ciliary activity is impaired and they begin to fill the alveoli. Eventually type II pneumocyte hyperplasia and extensive alveolar damage occurs; If the organized debris cannot be cleaned, fibrosis starts in the lung parenchyma after the second week. On the other hand, as muco-ciliary activity is impaired, upper respiratory tract bacteria also descend into the alveoli with micro-aspirations, causing bronchopneumonia. In post-mortem examinations, bronchopneumonia foci caused by bacteria and sometimes fungi are observed in most of the patients. COVID-19 pathogenesis consists of different stages. It can be divided into three stages from the onset of symptoms. The hallmark of the first seven days is viral activity. Although RT-PCR positivity continues, infective virus cannot be detected after the eighth day of the disease. The peak of the activity of dendritic cells, CD4 and CD8 T lymphocytes as well as the destruction of the cells infected by the virus within 3-5 days plays a role in the end of the viral activity period. T lymphocytes are responsible for the clearance of the virus, and their activities peak at the end of the first week. In post-mortem examinations, two more stages are defined after the end of viral activity. These stages are intertwined and differ from patient to patient. After the end of viral activity, the debris becomes organized and cleared in patients with a severe clinical course, and after about the second week, fibrosis and necrotizing pneumonia draw attention.

As a result; Antiviral therapy should be administered within the first week of viral activity. No significant benefit should be expected from antiviral treatment after viral activity ends. The extent of the damage and the regeneration ability of the host determine the fate of COVID-19. Regeneration ability decreases with age. Therefore, advanced age is among the important parameters that have an effect on the severity of the disease.

EPIDEMIOLOGY

In December 2019, the Chinese Center for Disease Control and Prevention and Wuhan city health authorities reported an outbreak of pneumonia of unknown cause in Wuhan City. On January 7, 2020, the Chinese Center for Disease and Control detected a new coronavirus from patients' lower respiratory tract samples, and announced on January 11 that it showed a genomic sequence. This novel coronavirus was later named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) named this infection caused by SARS-CoV-2 identified in 2019 as COVID-19.

It has been shown that this disease is transmitted from person to person, especially adults are susceptible to COVID-19 and the severity of the disease is related to age. At the same time, hypertension, diabetes, cardiovascular disease, etc. The disease has been shown to be more severe in people with comorbidities. In a study by Chen et al, examining 99 patients hospitalized in the same hospital with the diagnosis of COVID-19, they showed that older men were more likely to become infected and rapidly entered acute respiratory distress syndrome (ARDS), which created a life-threatening situation. In a study where comorbidities were analyzed, it was shown that approximately 17% of the patients had hypertension, 8% had diabetes, 5% had cardiovascular diseases and 2% had respiratory system diseases.

Many respiratory viruses show seasonal characteristics, the best known of these is influenza. While some scientists think that COVID-19 may have a seasonal characteristic and will decrease with the warming of the weather, some scientists think that this virus is not similar to the influenza virus and will not be affected by the season, presenting the disease as a supporting evidence for the occurrence of the disease in hot regions. There is not enough evidence to say that this virus may show a seasonal characteristic.

CLINICAL FINDINGS & TREATMENT

As a result of the studies carried out during the pandemic process, new information about the natural course of COVID-19 are added. Common symptoms of infection are respiratory symptoms, fever, cough, and dyspnoea. Symptoms such as headache, sore throat, runny nose, muscle and joint pain, extreme weakness, new sense of smell and taste, diarrhea can also be seen. Although the disease can be asymptomatic, in severe cases, pneumonia, severe acute

respiratory tract infection, kidney failure and even death may develop. While the fatality rate was 11% in the SARS epidemic and 35-50% in MERS-CoV, the fatality rate was reported as 3.8% according to the COVID-19 report of the People's Republic of China. This speed is 2.6% in our country as of May 2020.

Asymptomatic infection: In the literature, quantitative RT-PCR (nasopharyngeal swab samples) test positivity has been reported in asymptomatic individuals in community screenings. In most of the asymptomatic cases, some symptoms have developed in the later stage of the infection, but there are also cases who are asymptomatic during the clinical follow-up period.

First Application

Characterized primarily by fever, cough, shortness of breath, and bilateral infiltrates on lung imaging.

Pneumonia is the most common serious symptom of COVID-19. There are no specific clinical features that can reliably distinguish COVID-19 from other respiratory viral infections. In a study examining 138 patients hospitalized with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of the disease were:

- Fever 99%
- Fatigue 70%
- Dry cough 59%
- Anorexia 40%
- Myalgia 35%
- Dyspnea 31%
- Sputum production has been reported to be 27%.

In the study conducted by Li et al on 425 cases, the contagiousness coefficient (R0) was estimated to be 2.2, which means that on average, each patient spread infection to 2.2 people. Generally, an outbreak will increase as long as R0 is greater than 1, and control measures aim to make R0 less than 1.

Other cohort studies from Wuhan with patients with confirmed COVID-19 have reported a similar set of clinical findings. However, fever may not be a universal finding. In one study, fever was reported in almost all patients, but very low-grade fever was <38 ° C in about 20%. Another study on 1099 patients from Wuhan and other regions in China found that fever (axillary temperature measured above 37.5^0C) was present in only 44 percent of patients at admission, but ultimately at 89 percent during hospitalization. In the first cohort studies from China, smell and taste disturbances (anosmia and dys-

geusia) were also reported as common symptoms in patients with COVID-19. In a survey of 59 patients with COVID-19 in Italy, 34 percent reported loss of either sense of smell or taste, and 19 percent stated that they lost both. Whether this is a hallmark of COVID-19 remains unclear.

Other, less common symptoms include headache, sore throat, and rhinorrhea. In addition to respiratory symptoms, gastrointestinal symptoms (eg. nausea and diarrhea) have also been reported; In some patients, these may also be the application complaint. In a systematic meta-analysis of studies reporting on gastrointestinal symptoms in patients with confirmed COVID-19, the prevalence of gastrointestinal symptoms was 18 percent overall; Diarrhea, nausea / vomiting or abdominal pain were reported in 13, 10, and 9%, respectively.

Dermatological findings in patients with COVID-19 are not well defined. There are rare reports of urticarial rashes and transient livedo reticularis.

TREATMENT

The structure and usage of antiviral drugs used in treatment will be explained under separate headings.

Favipiravir

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is licensed in Japan for the treatment of complicated influenza infections because it inhibits the reproduction of influenza virus (IC50 = 0.022 μg / mL). Favipiravir is 54% bound to serum proteins, metabolized in the liver and excreted in the urine. In in vitro experiments, Ebola is recommended to be used at a dose 50% higher than the recommended dose in phase III studies for influenza treatment in modeling based on the effect of Ebola virus reproduction at a density of 10 μg/mL . In a study conducted with the recommended dose (2x1600mg on the first day, then 2x600mg) in a severe COVID-19 patient, the favipiravir concentration was found to be below the measurement limit of 1 μg/mL, which is well below the lowest EC50 (9.7 μg/mL). Favipiravir recommended in phase III studies A = Early phase viral activity 1-7 days B = Organization of the debris 8-12 days C = Complications organizing pneumonia; necrotizing pneumonia 12 - 1 7 12 A B C 5 dose is for viruses with an IC50 value of ≈3.2 μM. However, IC50 values of favipiravir for SARS-CoV-2 were almost always above the working limits (> 100 μM), so no inhibition could be shown.

Ivermectin

Ivermectin is an anti-parasitic drug widely used in veterinary medicine. The US Food and Drug Administration has confirmed that ivermectin suppresses the replication of SARS-CoV-2 in vitro. However, even with a dose ten times the recommended doses, the desired lung tissue density cannot be achieved. Therefore, it is recommended that inhaler forms be developed and evaluated in clinical studies.

Lopinavir

Lopinavir is a viral protease enzyme inhibitor. In in vitro studies, the lopinavir / ritonavir combination was found to be effective for SARS-CoV and MERS-CoV at accessible doses (SARSCoV EC50, 17.1 μM). Consistent with the in vitro findings, lopinavir / ritonavir has been found to be effective in the treatment of SARS and MERS in clinical studies. In vitro studies show that lopinavir / ritonavir is highly effective on SARS-CoV-2. Pharmacokinetic studies show that a blood density of 10 μg / ml can be achieved with 2 x 400/50 mg lopinavir / ritonavir administration, which includes in vitro EC50 values. A mathematical model study evaluating the very high protein binding capacity of lopinavir / ritonavir has been claimed that the desired density may not be achieved in the lung tissue. In this respect, a loading dose on the first day of clinical use should be considered.

Remdesivir

Remdesivir is an effective nucleoside analogue to Filoviruses (Ebola, Marburg et al.). After parenteral administration, it passes from the blood to the tissues in a very short time and the active compound remains in the cells for a longer time.In vitro studies have shown that it inhibits the proliferation of RSV, MERS-CoV and SARS-Cov-2. When 10 mg / kg is administered parenterally, it reaches a density of 10 μM. There is evidence that the active metabolite accumulated in the cells will reach the effective concentration as a result of administration of remdesivirine as a single daily dose for two hours.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is used in the treatment of malaria. Hydroxychloroquine binds very poorly to proteins, rapidly spreads to tissues, and its half-life is reported to be 32 ± 9 days. Although its anti-viral mechanism

of action is not fully known, it is mainly pointed out that it pre-vents infection when cells are used before they become infected. It has been reported that the effective dose is reached when 2 x 400 mg is used for five days. The most important side effect is QT prolongation. It has been calculated that the daily dose that causes QT prolongation is 2x600 mg and above. QT prolongation occurred in an average of 3.6 ± 1.6 days in patients who received 400 mg on the first day and 200 mg thereafter.

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