REVIEW ARTICLE

Dexamethasone for Covid-19: A Literature Review

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ABSTRACT

SARS-COV2 commonly known as COVID-19 is a disease that has become a global pandemic since the beginning of the year in 2020. Symptoms that are related to COVID-19 are fever, cough, chest pain, weakness, a nd difficulty breathing. Some cases of patients also experience mild symptoms such as diarrhea, dizziness, nausea, and vomiting. COVID-19 firstly found with pneumonia patients has never been diagnosed in China. Pneumonia or acute respiratory disease is the main disease that supports the indication of COVID-19. The treatment has been given to COVID-19 patients one of which is antibiotics and other drugs as a symptom reliever. Dexamethasone is a corticosteroid drug given to patients with an acute respiratory system. In this article, we will discuss dexamethasone for therapy COVID-19 with some reviews of studies that have been done in patients with acute respiratory systems.

Keywords: COVID-19, Dexamethasone, SARS-COV2

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INTRODUCTION

China Health Authority reported cases of pneumonia that occurred in Wuhan City, Hubei, Central China, which was unknown etiologically on 31 December 2019 to the World Health Organization (WHO) (1). COVID-19 declared a global pandemic caused by a coronavirus by WHO on 11 March 2020 (2).

Cytokines produced in the body are used to control and eliminate primary infections in pneumonia patients. Organ dysfunction may occur due to the systemic inflammatory response. To prevent this, balanced and not excessive cytokines are needed. It also reduces the systemic complications of the inflammatory response and does not affect local inflation (7). Corticosteroids are good inhibitors of inflammation. Corticosteroids are often used in pneumonia patients. Glucocorticoids have the anti-inflammatory effect of inhibiting most pro-inflammatory genes encoding cytokines, inflammatory enzymes, chemokines, and restoring homeostasis (4). Based on cases in COVID-19 patients who are associated with pneumonia, a review is needed regarding corticosteroid treatment, especially Dexamethasone. In this article, we will review the feasibility of dexamethasone for COVID-19 patients based on a study of giving dexamethasone in pneumonia (ARDS) patients.

COVID-19

SARS-CoV-2 or better known as COVID-19 is a family of coronavirus that is divided into two subfamilies, namely Coronavirinae and Toronavirinae. Coronavirinae is divided into four general, namely Alphacoronavirus (Human coronaviruses 229E and NL43), Betacoronavirus (Human coronavirus HKU1, SARS coronavirus, and MERS coronavirus), Gammacoronavirus, and Deltacoronavirus (1). So far, what has been appalling from the coronavirus family are the SARS and MERS. COVID-19 was first reported in a traditional market, Wuhan, Hubei. It was reported early on that a possible link to this viral intermediary was a snake. However, researchers are currently re-examining several animals that are likely to be intermediaries for the COVID-19 virus (5).

SARS-CoV-2, which infects humans, is considered as Betacoronavirus. The results of the phylogenetic analysis of SARS-Cov-2 showed a close association between the virus MERS- CoV (similar to 50%) and two coronaviruses that resemble SARS bats (bat-SL-CoVZXC21 and bat-SL-CoVZC45) and are genetically different from SARS-CoV (79% similarity) (4, 6). Other studies have reported an association of this virus with BatCov RatG13. So, these studies can conclude that the original host of the COVID-19 virus, the possibility is the bats (1, 7). The spread of

the COVID-19 disease is very fast from one city to another to another country. COVID-19 attacks more men than women. The mechanism of transmission and replication of the coronavirus can be seen in Figure 1 (8). The fatality rate varies according to the age category. It was reported that the case fatality rate at the age of 70-79 years was around 8%, while at the age of 80 years and over, it was around 14.8%. This fatality rate is related to the pre-existing conditions of comorbidity. Some disease among them are 5.6% cancer, 6.0% hypertension, 6.3% chronic respiratory disease, 7.3% diabetes, and 10.5% cardiovascular disease (9).

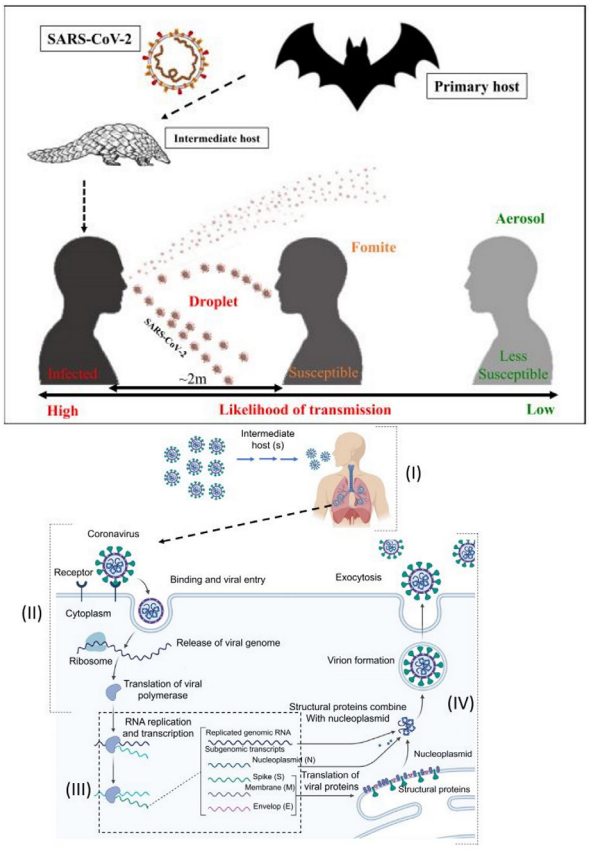

Figure 1 : Coronavirus spreading and replication mechanism (1).

Pneumonia

At the start of the outbreak reported in the previous study, seven samples of severe pneumonia patients undergoing treatment at the intensive unit of the Wuhan Jin Yin-Tan Hospital were sent to the WIV laboratory (Wuhan Institute of Virology) to diagnose the cause of the pathogen. As it is known that this outbreak occurred in winter and the same market environment as SARS infection, a primary pan-CoV PCR investigation was carried out to test this sample. From the PCR analysis, it was found that five samples were positive for CoV. Have been done remapped the total readings in this genome and obtained high coverage in the genome. This genome is called the 2019 novel coronavirus (2019-nCoV) by WHO. The four 2019-nCoV genome sequences (WIV02, WIV05, WIV06, and WIV07) are more than 99.9% identical (7).

Studies that have been conducted report an association of pneumonia and heart disease and often occur in the same patients. Have been reported heart complications in COVID-19 patients. The effects of COVID-19 on the cardiovascular system are the same and different as those of MERS and SARS. The most common comorbidities in COVID-19 patients are Cardiovascular disease. Increase cardiac troponin I (cTnI) result from Heart injury demonstrated has been confirmed in COVID-19 patients. Among COVID-19 patients, cardiovascular disease is the most common comorbid disease. The incidence of heart injury ranged from 7.2%-27.8% and case deaths, and the incidence in ICU patients was 77% and 22.2%. An increase in cTnI levels in a patient will result in a higher risk of cardiovascular disease. CTnI has increased significantly in COVID-19 patients who are severe or have died. High cTnI levels were also associated with higher mortality and complications. Patients with high cTnI levels were more likely to have higher NT-proBNP2 levels. These show a link between poor outcomes, heart dysfunction, and heart injury (6).

S. pneumoniae is detected in the myocardium in patients with severe pneumococci, resulting in cardiac injury and local pro-inflammatory response. Pneumonia is a highly pro-inflammatory disease and elevated levels of cytokines including procalcitonin, C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1beta (IL-1β), Interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), interleukin-8 (IL-8) which have been detected in COVID-19 patients especially in ICU patients. In infection control, cytokines play an important role, but they can also cause dysfunction and tissue damage so that the virus triggers the increased production of cytokines and a series of immune responses that can contribute to organ dysfunction and the systemic percentage in COVID-19 patients (2).

Dexamethasone

Dexamethasone is a synthetic glucocorticoid group. The structure of dexamethasone can be seen in Figure 2. Glucocorticoids are hormones produced by the cortex of the adrenal glands. This drug has analgesic, anti-inflammatory, and anti-allergic effects, and suppresses the immune system. Dexamethasone is

recommended for skin (erythroderma), blood diseases (idiopathic thrombocytopenic purpura), rheumatic and autoimmune diseases (rheumatoid arthritis, polyarthritis nodosa, systemic lupus erythematosus), respiratory tract diseases (bronchial asthma), tuberculosis meningitis (anti-infective therapy), palliative treatment of neoplastic disease, prophylaxis, and treatment of vomiting and nausea caused by antiemetic treatment and chemotherapy (10).

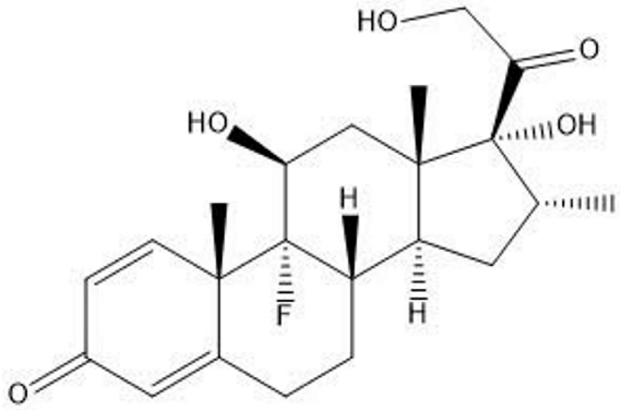

Figure 2 : Dexametason Structure (2).

Dexamethasone has a strong anti-inflammatory effect and a weak mineralocorticoid compared to other corticoids. So far, dexamethasone has never been evaluated in randomized controlled trials in ARDS patients even though dexamethasone is 20-30 times stronger than the natural hormone cortisol, and 4-5 times stronger than prednisone. Dexamethasone has a long-lasting pharmacological effect, allowing a one-dose per day regimen. The benefit of adding dexamethasone to supportive treatment is unknown in patients with ARDS. It has been reported that additional treatment with intravenous dexamethasone in patients with moderate to acute ARDS may weaken the pulmonary and systemic inflammatory matrix response and may decrease the duration of mechanical ventilation and all causes of death (11). In previous studies, it was reported that dexamethasone administration to ARDS patients can reduce the length of stay in the hospital. Also, dexamethasone has side effects in patients, namely gastric disorders and hyperglycemia (3, 11). Dexamethasone is also reported to have side effects, namely weight gain, such as fluid retention, some serious complication, and autoimmune.

A case report study reported by Hassan showed the effectiveness of dexamethasone in treating Covid-19 with ARDS. The study showed that there were 5 cases diagnosed with covid-19 pneumonia who were treated with 6 mg of dexamethasone. The results of this treatment suggest that dexamethasone can reduce the effects of COVID-19 with ARDS (13). Dexamethasone in the treatment of Covid-19 patients showed a reduction in mortality by up to 1/5 (20%) in patients on oxygen and up to 1/3 (35%) in patients on ventilators (14, 15). However, the use of dexamethasone in Covid-19 patients who have a history of diabetes or obesity requires extra supervision by a doctor because of the effects of increased blood pressure, hyperglycemia, and increased insulin that can be dangerous in diabetic patients. Therefore, the use of dexametasone in Covid-19 patients with diabetes is given at the right dose and also needs to consider the risks of its use (16).

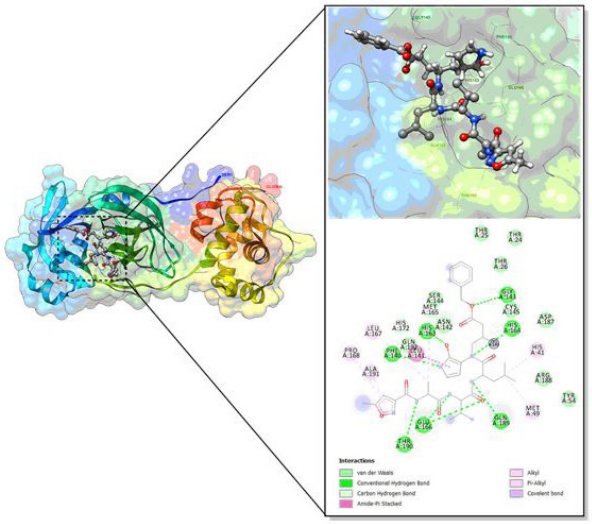

Figure 3 : Active Site of Main Protease COVID-19 (M^{pro}): PRD_002214-Mpro 2D and 3D Visualization (16, 17).

Many computational research has discussed the effectiveness of drugs for the treatment of COVID-19 targeted at proteases (Fig. 3) (17-20). See in Table I, dexamethasone has considerable effectiveness compared to other drugs for the treatment of COVID-19. This can be seen from the number of hydrogen bonds that occur between dexamethasone and the active site of the protease. In addition, it is also supported by the binding energy that occurs. The number of hydrogen bonds indicates that the stability of the complex formed between the drug and amino acids. Meanwhile, the binding energy shows the amount of energy required between the ligand and the receptor. A negative value on the energy means that the complex formation reaction between the drug and amino acids occurs spontaneously, and the greater the energy, the stronger the bonds that occur in the complex formed.

Table I : Drug-Receptor Interaction: Hydrogen Bond and Free Binding Energy

Drugs	PDB Code	Number of H-bonds	H-Bond Interaction (amino acid residue)	ΔG (kcal/mol)	Ref.
Dexamethasone	6LU7	4	Cys145, Cys145, His163, His164	-42.76	(16)
Betamethasone		2	Leu141, Gly13	-45.85	
Darunavir		2	Gly143, Glu166	-35.60	
Laponavir		1	Cys145	-40.66	
Dexamethasone	6W63	6	Gly143, His163, Glu166, Glu166, Gln19, Leu141	-38.73	(17)
Remdesivir		3	His163, Glu166, Phe140	-33.33	
Dexamethasone	6LU7	6	Asn142, Cys145, His163, Leu141,Phe 140, Ser144	-7.77	(18)
Hydroxychloroquine		2	Ala191, Gln192, Glu166, Gln189, Glu166	-7.28	
Festinavir		3	-	-7.15	
Oseltamivir		5	Gln189, Glu166, His41, Met165, Pro168	-7.01	
Chloroquine		1	-	-6.93	
Remdesivir		5	-	-6.77	
Azithromycin		3	-	-6.14	
Favipiravir		7	-	-4.78	

CONCLUSION

Pneumonia is a disease that is often associated with people with COVID-19. Dexamethasone is a synthetic glucocorticoid that has been tested in pneumonia patients. Dexamethasone can decrease length of stay and may decrease the duration of mechanical ventilation in COVID-19 ARDS patients. The complex formation of dexamethasone and amino acids on the active site of the protease was computationally stable and better than other drugs. Dexamethasone can be further investigated for the treatment of COVID-19 by considering the side effects it causes, such as gastric upset and hyperglycemia.

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