Inflammatory Mechanism and Clinical Implication of Asthma in COVID-19

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ABSTRACT Asthma is a chronic inflammatory disease of the respiratory tract that has become a public health problem in various countries. Referring to the Global Initiative for Asthma, the prevalence of asthma continues to increase especially in children. Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that has declared a pandemic by the world health organization on March 2020. For many years, it has been known that people with asthma have a worse impact on respiratory viral infections. Asthma has been listed by the centers for disease control and prevention as one of the risk factors for COVID-19, although several studies have different results. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as its cellular receptor, and it has been known that the expression of the ACE2 receptor is reduced in asthma patients. This reduced expression could also be accounted from the therapy of asthma. This paper aims to discuss the pathophysiology of asthma and COVID-19 and the susceptibility of asthma patients in contracting COVID-19.

KEYWORDS: Asthma, COVID-19, ACE2

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Introduction

Asthma has now become a public health problem in various countries that can reduce productivity and quality of life.[1] Asthma is a chronic inflammatory disease of the respiratory tract involving a vast number of cells, including eosinophils, epithelial cells, mast cells, macrophages, neutrophils, and T lymphocytes. In susceptible individuals, the inflammatory process causes repeated wheezing, shortness of breath, feeling of pressure on the chest, and coughing, especially at night and/or early morning.[2–4]

Referring to the Global Initiative for Asthma in 2020, there is an increasing prevalence of asthma in many countries, especially in children.[3] The prevalence of asthma is also higher in children born by cesarean delivery than children born vaginally.[5,6] Based on Riset Kesehatan Dasar (Riskesdas) data in 2018, the prevalence of asthma in Indonesia has decreased to 2.4% compared to 4.5% in 2013.[7]

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease began with the emergence of pneumonia case of unknown etiology in Wuhan, China at the end of December 2019.[8] The outbreak was thought to be initially started via zoonotic transmission, but latter it is known that human to human transmission is responsible for the following outbreak.[9] This virus comes from the same family as the viruses that cause SARS and Middle East Respiratory Syndrome (MERS), but SARS-CoV-2 is more contagious than the two. SARS-CoV-2 infections bear similar clinical features with SARS and MERS infection, although the former had prominent upper respiratory signs and symptoms. On March 11, 2020, the world health organization has declared COVID-19 a pandemic.[10,11] Indonesia reported the first case on March 2, 2020. Cases are increasing and spreading rapidly throughout Indonesia. As of July 9, 2020, the Ministry of Health reported 70,736 confirmed COVID-19 cases with 3417 deaths (case fatality rate (CFR) 4.8%).[12]

Centers for Disease Control and Prevention (CDC) reported that individuals over the age of 65 and those suffering from chronic diseases fall into the COVID-19 risk group.[13] In addition, it is also reported that people with moderate to severe asthma fall into this risk group, however, asthma is classified as a low risk in COVID-19 cases, especially in serial case reports in China. In a study evaluating the clinical and allergic characteristics, out of 140 patients in Wuhan, no cases of asthma and allergic rhinitis were reported, but only 2 cases of urticaria were reported.[14,15]

The literature study conducted by Nauhan in 2020 stated that asthma or allergies may not be a risk factor for COVID-19. In allergic asthma, there is a decrease in the number of angiotensin-converting enzyme 2 (ACE2) receptors in the body that are bound by SARS-CoV-2 so that they can provide protection against COVID-19.[16] However, other researchers reported that asthma patients had a higher risk of dying from COVID-19 in the hospital.[17] It is not yet known whether the SARS-CoV-2 virus can cause asthma attacks. In previous studies, it was reported that respiratory viruses such as rhinovirus (RV), respiration syncytial virus, herpes simplex virus, enterovirus (EnV), influenza (IfV) are the viruses that cause asthma attacks most often. However, there was no correlation between previous coronavirus pandemics (SARS-CoV and MERS-CoV) and asthma attacks.[18]

In this literature review, the relationship between asthma and COVID-19 will be presented regarding of risks, pathophysiology, level of asthma control, treatment, and mortality.

Asthma Pathophysiology

Asthma is a chronic inflammation of the respiratory tract involving various cells and cellular elements. Chronic inflammation is associated with airway hyperresponsiveness resulting in repeated episodes of chest tightness, wheezing, shortness of breath, and coughing, especially at night or early morning. The airway hyperresponsiveness in asthma is thought to be the effect of abnormal behavior of airway smooth muscle (ASM), increased release of mediators, edema, and irreversible ASM thickening. Asthma symptoms are varied, multifactorial, and potentially associated with bronchial inflammation. Evidence that inflammation is a component of asthma is the finding of eosinophil infiltration, neutrophils, mast cell degranulation, thickening of the sub-basal membrane, loss of epithelial cell integrity, mucus obstruction of the bronchial lumen, and goblet cells hyperplasia at autopsy performed in asthma patients.[19,20]

Traditionally, asthma was divided into allergic and non-allergic types based on the presence of IgE antibodies to certain allergens. Both are characterized by the airway infiltration of T helper (Th) cells.[21] The immunopathophysiology of asthma involves both innate and adaptive immunity. The inflammatory cells that play a role are especially eosinophil cells, mast cells, neutrophil cells, and T lymphocytes. Most asthma patients show symptoms of atopy and a small proportion do not. The inflammatory response in asthma patients varies between individuals, whether it is a rapid or slow inflammatory response. Mast cell degranulation in the airway is a rapid response by releasing inflammatory mediators and various metabolites that directly cause smooth muscle hyperresponsiveness resulting in airway obstruction within 15-30 min and will disappear within 2-3 h. Asthma response characterized by bronchoconstriction occurs after 3-4 h of allergen inhalation and may last up to 24 h.[20,22]

One of the most important mechanisms in the pathophysiology of asthma is airway remodeling. The correlation between airway remodeling and inflammation is not yet clear, but it is thought that these events may act as complementary processes rather than being cause and effect.[23] The inflammation could provoke injury of the airway epithelium, which is repaired via a repair cycle by recruiting various cell types toward airway remodeling. This remodeling has been associated with extracellular matrix desposition and is expected to mildly influence the baseline respiratory mechanics as well as potentially irreversible airway narrowing.[24–26] One of the most important features of airway remodeling is basal smooth muscle remodeling. After being stimulated, the cells of the basal smooth muscle will release varieties of cytokines and chemokines, such as chemokine (CXCL10; IP-10) and CX_3CL1 (Fractalkine) that will activate an auto-loop mechanism. Following this event, mast cells will penetrate and adhere to the basal smooth muscle cells.[27] Mast cells in turn will undergo activation and degranulation, both in an allergen-dependent and independent manner. This mast cells activation will eventually be responsible for inflammatory products disposition and facilitating the increase in basal smooth muscle mass as well as bronchial hyperresponsiveness.[28,29]

Most asthma is dominated by type-2 inflammation (type-2 T helper lymphocyte). Type-2 inflammation is associated with particular cytokines interleukin (IL-4, IL-5, and IL-14) and inflammatory cells.[30] A rise in inflammatory cells (especially mast cells, eosinophil cells, and lymphocytes) is associated with a slow type response that releases various mediators including prostaglandins, leukotrienes, and a number of proinflammatory cytokines, including IL-3 and IL-4, and tumor necrosis factor-alpha (TNF-α) from mast cells; IL-3, IL-5, TNF-ε, and granulocyte macrophage-colony stimulating factor (GM-CSF) from eosinophils; IL-1, TNF-α, interferon (IFN)-β, and GM-CSF from macrophages; and IL-6, Il-8, TNF-α, GM-CSF, and platelet-derived growth factor from the airway epithelial cells. In children suffering from asthma conditions, peripheral eosinophilia is associated with increased frequency of exacerbations. Figure 1 shows a slow type response and the various cytokines involved will cause local and systemic effects resulting in stimulation and mobilization of other inflammatory cells to the airway.[19,20,22]

COVID-19 Pathophysiology

The cause of COVID-19 is a virus belonging to the coronavirus family of the genus betacoronavirus. Coronavirus is a positive, encapsulated, and unsegmented single-stranded ribonucleic acid virus. The entry of CoV cells into the body is an intricate process involving receptor binding and proteolysis which leads to cell-virus fusion. There are 4 main protein structures in CoV, namely: Envelope/sheath (E), Membrane (M), Nucleocapsid (N), and Spike Protein (S).[31]

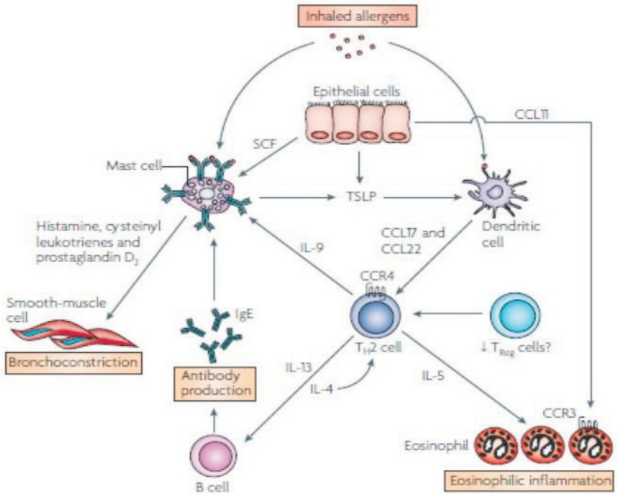

Figure 1. Inflammation and the immune cells involved in asthma.[19]

The S Protein intercedes receptor binding on the host cell membrane via the Receptor Binding Domain of the S1 domain and membrane fusion via the S2 subunit. ACE2 is a cellular receptor for SARS-CoV and SARS-CoV-2. ACE2 is expressed in the upper respiratory system, type I and II epithelial cells in the lung, endothelial cells, heart, enterocytes, renal tubular epithelium, and pancreas (Figure 2). Whether or not SARS-CoV-2 binds to additional sites needs further investigation. After binding to ACE2, the proximal serine protease, transmembrane protease serine 2 (TMPRSS2) is involved in protein S priming and Spike cleavage.[32,33] The gene expression of (ACE2) and TMPRSS during SARS-CoV-2 are determined by gender, comorbidity, age, and allergic inflammation type-2. After this cleavage, proteases, such as Furin then secretes spike fusion peptide and cellular viruses will enter through the endosomal pathway. A condition with low pH and the presence of proteases, such as the characteristics of cathepsin-L in the endosome microenvironment, will encourage further transport of the SARS-CoV-2 gene into the cytosol, which further viral replication leads to the formation of mature virions and subsequent spread.[31]

The inflamed cells will go through apoptosis or necrosis and will set off an inflammation response characterized by the stimulation of proinflammatory cytokines or chemokines, leading to the engagement of inflammatory cells. CD4+T Helper (Th1) cells manage the antigen presentation and immunity to CoV through the production of IFN-γ. Th17 cells induce neutrophils and macrophages recruitment by releasing IL-17, IL-21, and IL-22. SARS-CoV-2 infects immune cells circulation and escalates lymphocyte apoptosis (CD3, CD4, and CD8+T cells), causing lymphocytopenia. The severity of lymphocytopenia is related to the severity of SARS-CoV-2 infection. Lower T cell function reduces inhibition of the innate immune system and leads to a large amount of inflammatory cytokines released, known as "Cytokine Storm". Verily, the amount of circulating cytokines/chemokines (IL-6, CXC-chemokine ligant 10, and CC-chemokine ligand 2) correlates with cytokine storm syndrome. Elevated levels of these cytokines/chemokines may play a role in the hyperinflammation caused by SARS-CoV-2, leading to multiple organ failure.[31]

Asthma and Covid-19

The symptoms of severe asthma or exacerbations and COVID-19 will be very similar. The difference is the presence of fever in COVID-19 patients, although actually in asthma patients, virus-induced exacerbations can also cause fever. In addition, other symptoms that are sometimes found in COVID-19 patients include myalgia, headache, pharyngitis, nasal congestion, anosmia, diarrhea, nausea, and vomiting. History of traveling, history of contact with probable or confirmed COVID-19 patients, and the lack of atopic history can also lead to COVID-19.[34–36]

Infants and younger children tend to be at higher risk for hospitalization due to viral respiratory tract infections. Literature stated that COVID-19 infection in children with asthma has a higher risk of developing pneumonia and acute respiratory disease.[13,37] In addition, COVID-19 infection in children with asthma can also cause easy induction of viruses that trigger an exacerbation of asthma. However, there is very little literature on this subject. Based on the existing information, it is not certain whether there is a higher risk of COVID-19 morbidity in children with asthma.[38]

For 18 years it has been known that people with asthma have a worse impact on viral infections such as the flu compared to people without asthma.[39] Uncontrolled asthma will cause

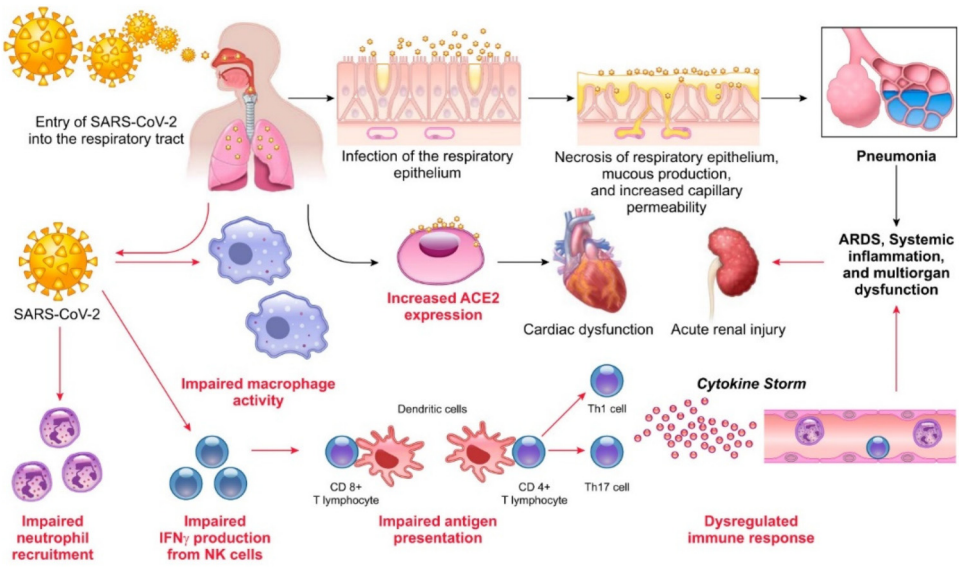

Figure 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptors in human.[31]

worse asthma exacerbations.[40] Various studies have reported that there is an impaired function of epithelial cells and leukocytes from people with asthma in producing antivirals such as pulmonary IFN-α, IFN-β, and IFN-λ. This IFN deficit could hinder the ability of the patient's innate immunity to prevent the spread of the viruses to the lower respiratory tract hence increased the severity of asthma exacerbations. Based on this, asthma should be recognized as a risk factor for the severity of COVID-19.[41–44]

Asthma has been listed by The US CDC as one of the risk factors for severe COVID-19 disease. This is because various respiratory viruses have been shown to invoke severe symptoms in people suffering from chronic airway disorders, such as asthma.[45] On the other hand, in the case series reports in China, asthma and respiratory allergies have not been recognized as consequential risk factors for the severity of COVID-19.[16] There are also emerging concerns regarding the risk of intubation in COVID-19 patients with underlying asthma conditions. A recent study conducted in the U.S. however, suggested that asthma does not increase the risk of intubation in COVID-19 patients, even after adjusting the body mass index and sex variable.[46] On the contrary, another study reported that asthma was significantly associated with longer intubation period in the age group of 18-49 years and 50-64 years, and not in age group >65 years old. Although in this same study asthma was not associated with a higher mortality rate.[47]

In SARS-CoV-1 infection, disease severity was associated with the initial expression of type I IFN along with elevated levels of IFN-related CXCL10 and IFN-ɣ.[48] This disorganized and hyperactive innate response can block the protective adaptive immune response as described by Richardson in COVID-19 patients and was seen in a mouse model with SARS-CoV infection in which an initial (absent/low) IFN signal would be of benefit in preventing infiltration of monocytes/macrophages in the lungs, vascular leakage, cytokine storm, and abnormal T-cell response.[49,50]

Production of antiviral IFN by virus-infected airway cells is significant in the initial defense facilitated by innate antiviral immunity against SARS-CoV-2, a virus whose immune response we do not recognize. Therefore, treating/preventing the severity of COVID-19 with azithromycin in asthma patients substantially increase IFN production by airway cells upon SARS-CoV-2 infection will be very effective in reducing the risk of severity. This is supported by clinical trials evidence which suggests that azithromycin prevents exacerbation of asthma (most of which are caused by viruses) and is efficacious in preventing severe lower respiratory tract viral infections in younger children.[51,52] This is also backed up by an investigation of COVID-19 patients without asthma (asthma is not addressed in the report), which suggested a significantly higher advantage in six patients with SARS-CoV-2 that are given azithromycin and hydroxychloroquine, in comparison to those with hydroxychloroquine alone (although the reason for the administration of azithromycin is "to avert secondary bacterial infection," not because of its nature that induces virus-specific IFN).[53]

The use of azithromycin (but not erythromycin or telithromycin) can predominantly increase the production of IFN-β and IFN-λ from RV-infected human bronchial epithelial cells in vitro.[54] Azithromycin induced the production of IFN-β and IFN-λ by virus-infected bronchial epithelial cells, which also proved that this was a variable among the 225 new macrolides studied. One IFNs-induced macrolide was equivalent to fivefold and was known to significantly ($P = .023$) dampened viral replication in people with asthma. Hiles *et al.* investigated the effect of azithromycin on asthma exacerbation in both allergic and nonallergic asthma. Although improvements could be seen in both groups compared to the group that was not given azithromycin, the result was not statistically significant.[55,56]

There are additional molecules of innate immunity besides IFNs that also possess antiviral functions generated by alveolar type-2 cells, such as surfactant protein A, surfactant protein D, and mannose-binding lectin. The concentration of these molecules is increased in patients with chronic inflammation as seen in asthma and respiratory allergy. These molecules are found to bind the spike protein of SARS-CoV-2, inhibiting its interaction to the ACE2 therefore are able to prevent the alveolar macrophage from activation by the virus.[57,58]

In addition, the increased eosinophils in asthma may be beneficial in COVID-19-infected lungs. Eosinophils are diminished in the peripheral blood of patients infected with COVID-19. The increasing number of eosinophils in the airway of asthma patients may protect against the excessive inflammatory response of the severe COVID-19 phenotype.[14]

SARS-CoV-2 utilizes ACE2 as its cellular receptor, as does SARS-CoV.[28] Increased ACE2 expression enhances *in vitro* vulnerability to SARS-CoV and researchers examining factors affecting ACE2 gene expression reported that an increase in ACE2 expression was associated with smoking, hypertension, and diabetes which in turn was correlated with an increase in the severity of COVID-19.[59,60]

Respiratory viral infection is a frequent trigger of severe asthma exacerbation in children and adults. A large-scale epidemiological study of the COVID-19 in China did not include asthma as a risk factor of severe COVID-19 disease.[61] Investigations of asthma in COVID-19 continue to give different results. Although many have stated that asthma could increase the risk of severe COVID-19 infections, plenty has also suggested asthma as a protective factor of COVID-19 infection. According to Jackson *et al.*, one reason that is strong enough to prove that asthma and other allergic diseases do not have the potential to cause severe COVID-19 is the reduced expression of the ACE2 gene in airway cells and this can lower the rate of SARS-CoV-2 infection.[45]

Other researchers reported that allergy and controlled exposure to allergens in the airway was associated with a significant decrease of ACE2 expression. The lowest ACE2 expression was found in people who had a high level of allergy sensitivity and asthma. Different results could be seen in patients with nonallergic asthma as nonallergic asthma was not associated with decreased ACE2 expression.[49,62] Keswani *et al.* investigated the difference between COVID-19 cases among allergic and nonallergic asthma. The study showed that nonallergic asthma was associated with an increased risk of COVID-19 infection, disease severity, and the risk of intubation. However, there are also additional factors besides ACE2 expression that can modulate the COVID-19 response in individuals with allergies, but there has been no further research on this.[45,63]

Although ACE transforms angiotensin I (Ang I) to angiotensin II (Ang II) which is a potent decapeptide and vasoconstrictor, ACE2 catabolizes Ang II to Ang-(1-7) in kidney and other tissues. Therefore, ACE2 is believed to be a natural prevention of the unvaforable effects of ACE and Ang II in the pathophysiology of hypertension, kidney disease, diabetes mellitus, and lung injury.[64,65] It is also important to consider the presence of other comorbidity coexistent with asthma that could possibly increase the risk of severe COVID-19. Hypertension is one of the contributing factors for COVID-19, but there is no increase in ACE2 in asthma patients with or without hypertension.[66] Heffler et al. investigates the risk of COVID-19 in asthma patients with other comorbidities. From this study, patients with asthma and type-2 diabetes mellitus had a higher incidence of COVID-19 compared to asthma only. While other condition such as bronchiectasis, obesity, gastroesophageal reflux disease, and cardiovascular disease has no significant differences in COVID-19 incidence.[67]

TMPRSS2 is a transmembrane protease that modifies spike protein in several viruses—including SARS-CoV, SARS-CoV-2, MERS-CoV, and influenza A and B—to promote viral infection and spread. Researchers found the expression of the TMPRSS2 gene was much higher than the expression of the ACE2 gene in COVID-19 patients on sputum cell examination.[68]

Uncontrolled asthma will very easily provide entry to the virus, which will worsen asthma exacerbation, on the other hand, controlled asthma can reduce the severity of COVID-19.[40] One of the concerns regarding the management of asthma in times of pandemic is in differentiating whether the symptoms are caused by asthma or SARS-CoV-2 infection. In the early COVID-19 stage, the symptoms may be overlapping with those of asthma, although later it might progress to somewhat clearer symptoms.[69,70] Nevertheless, all methods to control asthma, whether using inhaled steroids, a combination of inhaled steroids and bronchodilators, or monoclonal antibody therapy has been shown to substantially reduce the risk of exacerbation (mostly due to viral induction). All asthma therapy protocol should be continued to optimize controlled asthma as this can also reduce the risk of worsening from COVID-19.[71]

The use of corticosteroid therapy in COVID-19 patients needs further attention because the use of corticosteroids can reduce the immune response in eliminating viruses and against the prevention of secondary infections from bacteria.[71] However, in asthma patients where there has been an inflammatory reaction due to allergies in the lungs, the use of topical steroids is actually needed to help the body deal with inflammation, so inhaled steroid therapy must be started immediately/continued if there are clinical symptoms of asthma in COVID-19 patients. These suggestions are also supported by a statement put out by the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics.[72,73]

The expression of ACE2 and TMPRSS2 was found lower in patients taking inhaled corticosteroid (ICS) than in those not. The study is based on concerns that the immunosuppressant effect of ICS could put asthma patients at greater risk during the COVID-19 pandemic. Lower expression of ACE2 and TMPRSS2 in patients with ICS therapy proves that ICS usage will not enhance the risk and severity of COVID-19. However, researchers did not find any difference between the number of ACE2 and TMPRSS2 expression in sputum cells before and 2-4 weeks after treatment.[73,74] Nebulization in asthma patients with COVID-19 is not recommended because nebulization is an aerosol procedure that can increase SARS-CoV-2 transmission. Turbuhaler or disc is recommended over nebulization for this case.[70,75] In addition, the use of oral steroids is also not recommended in COVID-19 because it will increase viral replication.[76] However, in patients with moderate to severe asthma, oral steroid use is allowed if the patient does not respond to bronchodilators and the benefit is greater when given oral steroids.[70,75,77]

The use of monoclonal antibody therapy in asthma has also sparked a new interest. As was known before, cross-linking of IgE and $Fc_{\varepsilon}RI$ could reduce the antiviral response in asthma patients, explaining the reason why asthma patients are at increased risk of respiratory viral infections. Omalizumab is the first monoclonal antibody therapy used in asthma cases. Omalizumab works by binding the circulating IgE and prevents it from binding to IgE receptors on the mast cells surface. By blocking IgE, the susceptibility of respiratory viral infection could be lowered by enhancing IFN-α signaling. Omalizumab could also decrease IL-33 which induces pro-inflammatory cytokines production such as IL-6, IL-1β, TNF-α, and prostaglandin. This antiviral property is also thought to be beneficial in COVID-19 cases. Especially since monoclonal antibody therapy has shown to be effective and safe.[21,78,79]

Several monoclonal antibodies have the ability to bind the spike protein of SARS-CoV-1 and due to the molecular similarity, are also able to bind the spike protein of SARS-CoV-2, inhibiting its binding to the ACE2, therefore, are able to protect the alveolar macrophage from activation by the virus. Recently there have been some efforts from various group to isolate the monoclonal antibody from B cells of patients that have recovered from SARS-CoV-2 infection. This effort has met a lot of challenges particularly in creating the stable monoclonal antibody that could work effectively. Although seems promising, the use of a monoclonal antibody in COVID-19 still needs a long way to go.[21,80]

The CDC's morbidity and mortality report remarks that of the 149,082 COVID-19 cases recorded in the U. S, only 2572 (1.7%) occurred in children aged 18 years and under.[81] The reported patients had certain risk factors, 23% of them had at least 1 risk factor including asthma, and 5.7% of the children with COVID-19 needed hospitalization (in comparison with 10% of adults aged 18-64 years), and only 3 deaths were recorded in children (<1% of pediatric cases). A case series of 72,000 cases in China reported that roughly 1% of those cases were children aged 0-18 years with 1 death reported in the adolescent population (none in children under 10 years of age).[61,82]

Conclusion

There is no satisfying evidence to support that asthma patients are at higher risk of becoming critically ill due to the 2019 coronavirus disease (COVID-19). As in the previous SARS outbreak, patients with asthma, especially children, were less susceptible to SARS-CoV with a low rate of exacerbation of asthma. In addition, several literature studies and researches have shown that asthma is not a risk factor for COVID-19. In allergic asthma, there is a decrease in the level of ACE2 receptors in the body bound to SARS-CoV-2 so that it can provide a protective effect against COVID-19.

Other than that, it is very important for asthma patients to maintain their treatment, whether with the use of inhaled steroids, a combination of inhaled steroids and bronchodilators, or corticosteroid monoclonal antibody therapy without making independent dose adjustments or stopping treatment. The use of azithromycin in COVID-19 patients with asthma is also considered effective because it can increase the production of IFN-β and IFN-λ, where this production is reduced in patients with asthma. Low levels of IFN can cause severe asthma exacerbation. Nebulation therapy needs to be avoided in asthma patients infected with COVID-19 because it is aerosolized so that it can increase SARS-CoV-2 transmission.

It is important for us to better understand these interactions, so that we can provide better protection for the most vulnerable people, including those in high-risk groups. Further research across all age groups is required to provide a better grip of the impact of an underlying condition, such as asthma, other allergic diseases, and T2 inflammation on COVID-19 susceptibility.

Author Contributions

Vasa Adi Wisnu Wardhana participated in the data curation, format analysis, investigation, methodology, project administration, visualization, and writing-original draft Alfian Nur Rosyid participated in conceptualization format, analysis, investigation, methodology, funding acquisition, resources, supervision, validation, writing-original draft, and writing-review and editing.

Ethical Approval

No ethical approval/patients consent is required.

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