Chapter

Asthma and COVID-19

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Abstract

Asthma is a heterogeneous disease developed against various stimuli (indoor and outdoor allergens, cigarette, air pollution, etc.), associated with airway hypersensitivity and characterized by chronic airway inflammation. COVID-19 is a disease caused by a coronavirus strain called Severe Acute Respiratory Syndrome-coronavirus-2 (SARS-CoV-2). There may be some clinical confusions in proper diagnostics due to certain similarities of both diseases's symptoms such as, for example, a difficulty of breathing, cough, and shortness of breath. The current data on asthma being a risk factor for COVID-19 are controversial. It has been reported that asthma is not a risk factor for COVID-19 as the course of COVID-19 in patients with asthma is similar to that observed in the normal population. On the other hand, a current guidance from the World Health Organization (WHO) suggests that asthmatic patients can get more severe illness from COVID-19. Moreover, as with all respiratory tract infections, SARS-CoV-2 virus can certainly impair asthma control. However, recent studies suggest a potential beneficial effect of corticosteroids on SARS-CoV-2 infection as they suppress type II inflammation and restore anti-viral immunity. Prolonged use of a high dose of systemic steroids can increase susceptibility to infection and the occurrence of systemic side effects. However, patients with asthma should definitely continue their prescribed treatment with inhaler steroids and other additional medicines they use during SARS-CoV-2 infection. In asthmatic patients infected with SARS-CoV-2, the most significant risk factor is the loss of asthma control and subsequent presentation to healthcare centers due to the lack of asthma control. Therefore, the asthmatic patients using biological agents are recommended to continue their prescribed treatment such as omelizumab, mopelizumab and prolong the treatment intervals during the peak of infection.

Keywords: asthma, COVID-19, pandemic, asthma treatment, inflammation

1. Introduction

COVID-19 is a disease caused by a novel *coronavirus strain* [1–10], which has been named by the *International Committee on Taxonomy of Viruses* (ICTV) as SARS-CoV-2. It has caused a severe viral pandemic worldwide since March 2020 [8, 11]. The virus was first reported in Wuhan, China. Its source is thought to be a live animal market, namely bats [12]. The transmission is via respiratory droplets [8, 9]. The mean incubation period is 2 to 7 days and the main symptoms include fatigue, shortness of breath, fever, coughing, loss of smell and taste, sore throat, muscle pain, headache, vomiting and diarrhea [2, 13]. The course of disease is highly variable. Comorbidities seen in infected individuals are important in terms of the healing time, going to intensive care, and affecting mortality. Among these

comorbidities, particular conditions such as hypertension, ischemic heart diseases, diabetes, and chronic obstructive pulmonary disease represent the most important risk factors for a severe course of disease [13, 14].

Asthma is one of the most common chronic respiratory tract diseases [15]. It is considered to affect approximately 300 million people across the world. Prevalence rates vary to a great extent, ranging from 1% to 18% in children and adults in different countries [16]. Asthma exacerbation is an important reason for emergency admission [15, 16]. It is defined by respiratory symptoms such as wheezing, shortness of breath, tightness in the chest and/or coughing and expiratory air flow limitation. These signs vary in in time. Usually, exacerbations are observed due to various factors like allergy or irritants, exercise, change of air or respiratory tract infections. Symptoms and airway limitation are frequently resolved with treatment or spontaneously and may be absent for weeks or months. On the other hand, such exacerbations may be life-threatening, i.e. the disease may have various clinical presentations and severities which are specific to each patient [16]. For an effective treatment and control of the disease, it is important to educate the patient and help to cooperate with the doctor. The education includes preparation of a written asthma action plan and medical evaluation at regular intervals. A written asthma action plan is a document prepared specifically for the patient by the doctor to show how to monitor his/her symptoms and respiratory functions at home, and it should be reviewed by the physician at regular intervals. This plan helps the patients recognize the aggravation of their asthma and use suitable treatment options [16]. This is very important for minimizing asthmatic patients' visits to healthcare centers during the pandemic and decreasing the risk of transmission [16, 17].

In pandemic the patients with asthma should be managed in two groups: the patients who have asthma but have not yet contracted COVID-19, and those who have asthma and have contracted COVID-19 [18]. COVID-19 and subsequent association between asthma and COVID-19 is a challenging clinical condition with more questions than answers. However, we can make some predictions based on the available data.

2. Management of a patient with asthma who has not contracted COVID-19

The main objective for patients should be to avoid COVID-19 infection. At first, the patient should be informed that asthma does not pose an extra risk for contracting COVID-19 as well as leading to a severe course of disease [19, 20]. Social isolation and adherence to hygiene rules are the most important factors in prevention of disease transmission. Patients with asthma are recommended to remain isolated in their home environment, if possible. They should be instructed to self-monitor symptoms using a PEFmeter [21]. Thus, visits to healthcare centers should be kept at minimum. If patients do not have serious problems during this period, scheduled visits should be delayed as much as possible and physicians should be consulted by telephone, if necessary. In case of any increase in coughing and/or shortness of breath, first of all, it should be made sure that the bronchodilators are delivered at adequate doses and the bronchodilator device (nebulizer) is used correctly. The patients should be instructed by their physician about what to do when their asthma gets worse by means of a written action plan. Considering that an asthma patient who1 is on a control-visit may be a potential COVID-19 carrier, it is very important not to perform a respiratory function test unless it is extremely necessary. Otherwise, it is recommended to keep the room very well ventilated, provide the test technician with appropriate protective equipment, particularly an N95 mask, and perform the test in a negative pressure room, if possible [22].

Approximately 80% of patients with asthma have allergic rhinitis and approximately 40% of patients with allergic rhinitis have allergic asthma. It is important to keep the symptoms of allergic rhinitis under control for control of asthma [22–24]. Patients with allergic rhinitis can also use their nasal steroids and antihistamines safely during this pandemic [23, 25]. During the quarantine, patients may have trouble gaining access to their medications due to outgoing restrictions and risk of contamination. In Turkey, the validity of the medication reports for patients with asthma has been extended from March 1st, 2020 by the Turkish Ministry of Health and Social Security Institution so that patients can obtain their medicines from pharmacies without prescription [8]. The validity of disability reports has been also automatically extended. If patients with allergic rhinitis do not use their drugs for symptom control especially during the pollen season, their sneezing will increase. The same also applies for patients allergic to house dust mites. Spring time poses a risk for asthma attacks in patients with pollen allergy while similarly prolonged isolation and quarantine is a risk factor for an attack and loss of asthma control in asthma patients allergic to house dust mites. If patients with pollen allergy follow the rules of isolation and avoid going out, their symptoms will be under control due to reduced contact with pollens. These patients should ventilate their rooms in the afternoon and, if they have to ventilate it in the morning, they should stay in another room. In patients with allergic rhinitis who use masks effectively when they go out, exposure to pollens will be reduced and thus their symptoms and the need for medications will also be decreased. Patients with allergic rhinitis sensitized to house dust mites are unfortunate during this period because of a prolonged stay in closed environments. Therefore, it is very important that they use their allergic rhinitis medications regularly and follow the measures to protect themselves from house dust mites. While hand disinfectants containing chlorhexidine are not effective in SARS-CoV-2 [26], they may also lead to asthma attacks in those allergic to this chemical [26]. Use of latex hand gloves for hand hygiene may also lead to asthma attacks in patients with latex allergy, therefore the washing hands with soap and water should be preferred [26].

As a result asthma patients who have not contracted COVID-19 should definitely continue their inhaler steroid treatments and additional prescribed medications, and should follow the protection and hygiene rules as much as possible even when they are clinically stable [8, 16]. Discontinuation of controlling medications leads to disease exacerbation, increases the risk of having an asthma attack and eventually poses a higher risk for SARS CoV-2 contamination by hospital admission. Doses of inhaler steroids should not be reduced even when asthma is under control. The disease may also be controlled with non-steroidal treatments in some patients with asthma. In these patients, other treatments should be continued without steroids or in combination with low dose steroids [18]. Systemic steroids should be used as short as possible in patients with severe asthma. Because in long-term use, susceptibility to infection and steroid side effects may occur [15, 18].

3. Management of a patient with asthma who has contracted COVID-19

Pathophysiology of the coronaviruses (CoVs) and asthma comorbidity is complex and many aspects are unknown. In this book chapter we review the available literature on the pathogenesis of asthma and COVID-19.

Asthma is characterized by chronic airway inflammation [16], mainly a type 2 inflammation. Type 2 immunity involves helper T cells (Th 2), type 2 B cells, type 2 innate lymphoid cells, type 2 macrophages, IL-4 releasing natural killer (NK) and natural killer T (NKT) cells, basophils, eosinophils and mast cells [3, 4]. In general,

antiviral and allergic responses are two separate branches of immunity and interact in a comprehensive network of interactions. Type I IFNs are the family of antiviral cytokines that play an important and central role in this network. In asthma, release of type I IFNs from bronchial epithelial cells and plasmacytoid dendritic cells is disrupted [3, 4].

It is well known that eosinophils play a central role in allergic diseases including asthma [4]. The possible effects of eosinophils on CoV are also remarkable. Eosinophils have a potential role in enhancing viral clearance and antiviral host defense. Recombinant eosinophil-derived neurotoxin (a major eosinophil ribonuclease) is capable of reducing the infectivity of respiratory syncytial virus (RSV). In addition, eosinophils can be activated with ssRNA through triggering the TLR-7-MyD88 signaling pathway, which might result in RSV clearance and limitation of virus-induced lung dysfunction. The low prevalence of COVID-19 in asthma patients may be due to eosinophils' defense against the virus. Eosinopenia occurs in COVID-19, pathophysiology is unclear [27]. Blockade of eosinophil release from bone marrow during acute infection, decreased expression of chemokine receptors or direct eosinophil apoptosis may caused by type 1 IFNs may be responsible. There is little indication that eosinophils play a protective or aggravating role during SARS-CoV-2 infection. Eosinopenia, however, may be a prognostic indicator for more severe SARS-CoV-2 infection [27]. Additionally, it is not known whether eosinopenia is a consequence of impaired immunity or biologics intake. The role of eosinophils in the course of eosinophilic inflammation associated with SARS-CoV-2 infection and allergy needs to be investigated further [4].

In theory, asthma as a lung-targeted chronic disease should increase the vulnerability of lung tissue to COVID-19 infection and should lead to a worse course of COVID-19 and reduced anti-viral immune response. But, interestingly, it was reported that asthma produces a type 2 inflammatory cytokines (IL-4,-5 and – 13) and accumulation of eosinophils in the airways and their number increases systemically, what provides a protection against COVID-19 [4]. As with SARS and other seasonal coronaviruses, SARS-Cov-2 also uses the cellular receptors of angiotensin converting enzyme 2 (ACE2) to invade the cells. Upregulated ACE-2 expression increases the sensitivity of receptor-expressing cells to infection. However, ACE-2 expression in the respiratory tract epithelium is decreased in patients with asthma as compared to normal control subjects, and this protects from COVID-19 [4, 5, 28]. Allergic diseases do not predispose to COVID-19 and does not increase COVID-19 severity. Asthma also does not pose a risk to COVID-19, and there is no difference between asthma patients with and without COVID-19 in terms of hospital admission and severity of the course of disease [15, 28–30]. When patients with asthma contract COVID-19, they have a disease course similar to that of the normal population [15, 31]. But as with all viruses causing respiratory tract infections, SARS-CoV-2 is also a risk factor for asthma attacks and disrupts asthma control [16, 32]. Despite proper and adequate treatment bronchodilator therapy, patients with increased symptoms, additional symptoms and/or contact history should be admitted to the hospital and undergo appropriate examination and investigations.

Exacerbation of asthma and allergic rhinitis may also be confused with COVID-19 clinically [8, 23]. Dry coughs and shortness of breath may be seen asthma, allergic rhinitis and COVID-19. Seasonality of symptoms and history of symptom development in the presence of exposure to a certain allergic agent are quite helpful in the differential diagnosis of allergic rhinitis. Atopy test also supports the diagnosis. It is also very important to distinguish between an asthma attack and COVID-19 infection attack in a patient with a prior diagnosis of asthma as both display interfering symptoms such as shortness of breath and coughing. Therefore, differential diagnosis is extremely significant in the group of patients with such comorbidity.

In addition to the clinical presentation, laboratory findings (such as eosinophil and lymphocyte count, C reactive protein, D Dimer) may also be beneficial in the differential diagnosis. While presence of lymphopenia and eosinopenia in hemogram may favor COVID-19 [8] increased eosinophil levels may indicate asthma. While an asthma patient presenting with symptoms such as coughing, shortness of breath, wheezing and stridor without any additional finding should be primarily evaluated for an asthma attack; considering that everybody may be infected in such a pandemic, extra care should be exercised regarding social isolation, distance and the use of personal protective equipment for the safety of both patient and healthcare personnel [8]. Asthmatic patients who develop weakness, loss of smell and taste should have chest X-ray and blood tests for COVID-19 [8].

4. Symptoms of asthma, COVID-19 and allergic rhinitis

Corticosteroids hold a significant place in the treatment of asthma [2]. High-dose corticosteroids have been used α during the SARS and MERS outbreaks and in COVID-19 to suppress lung inflammation during critical illness of infected patients. Corticosteroids (inhaled or systemic) can inhibit production of the critical antiviral mediators type I and III interferons [3]). At the same time its suppress type 2 inflammation and their use in COVID-19-associated exacerbation may lead to the beneficial effect of secondary restoration of impaired antiviral immunity. However, clinical evidence of corticosteroid use in COVID-19 is still insufficient [3].

In patients with asthma who have contracted COVID-19, inhaled corticosteroid dose may be increased 4-fold depending on the severity of the disease or use of systemic administration of steroids is recommended [18, 30]. In patients with severe asthma, systemic steroid therapy should be used as short as possible, as in asthma patients without COVID-19.

Steroid therapy preferably should be taken in the form of metered-dose inhalers containing dry powder rather than nebulizers [5, 33]. Metered-dose inhalers are ideal devices thanks to their ease of use and low risk of viral transmission, but they may not be effective in cases of severe dyspnea, cognitive or neuromuscular disorders and respiratory failure with inadequate inspiratory strength [33]. Dry powder inhalers are able to reach the lungs in low inspiratory flow and do not require hand-breath coordination (squeezing the inhaler medication at the same time while breathing deeply). On the other hand, dry powder inhalers may lead to irritation in the airways and coughing, and a by creating aerolization potential viral transmission is also of question. It is contradictory whether the treatment with a nebulizer is risky in terms of viral transmission due to aerosolization [34]. As a result, a metered-dose inhalator with a valved reservoir or dry powder inhaler is preferred for reducing the auto-aerosolization and spread of the virus [35].

Leukotriene receptor antagonists with their beneficial anti-inflammatory and bronchodilator activities may also be added to the treatment of the patients with COVID-19 and asthma admitted to the hospital [5, 30, 36].

Azithromycin has been shown to be an effective treatment in decreasing the frequency of exacerbations and improving the quality of life in asthma patients whose condition cannot be controlled with standard treatment [31, 37]. Azithromycin decreases the risk of COVID-19-related severe outcomes by increasing the IFN production associated with a natural antiviral immunity in respiratory tract cells [37]. However, azithromycin is not recommended for prophylactic treatment of COVID-19 [37].

An asthma patient receiving allergen immunotherapy who is infected with COVID-19 or in contact with an infected person may continue to receive his/her

treatment in the absence of any symptoms [38]. It has been reported that immune response to virus can be improved and cytokine storm can be prevented by this treatment [4, 30, 39]. But if there are any signs of respiratory tract infection, it is recommended to treat this infection [39].

Use of Anti-IgE, anti-IL-5/IL-5 alfa, anti-IL-4 alfa is not risky for patient with asthma who has contracted COVID-19, therefore such medications may be safely used to control asthma [30, 40]. Although patients using biologic agents are recommended to continue their treatment. During the period of COVID-19 peak, biological agent treatment is applied less frequently. Biological agent therapy continues as before when symptoms are improved or COVID-PCR becomes negative [22, 23]. Since patients with severe asthma may be at higher risk of severe COVID-19 infection, they should avoid any activities which may disrupt their asthma control and they should use their asthma therapies properly.

In conclusion, asthma does not represent a risk factor for COVID-19 and asthma does not adversely affect the course of COVID-19. However, it is extremely important to keep asthma under control particularly during the pandemic period. Patients with asthma should be recommended to continue to use inhaler steroids that keep their asthma under control along with other prescribed medications. Patients should be provided with a written emergency action plan because nowadays a visit to a healthcare center carries a risk for the SARS-CoV-2 infection. In order to prevent the risk of transmission of infection, training should be given on maintaining social isolation and distance, avoiding contact, hand hygiene and correct use of masks.

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