REVIEW ARTICLE

ASTHMA IN A PATIENT WITH COVID-19: DOES IT PROTECT OR INCREASE THE RISKS?

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ABSTRACT
The aim: To investigate the impact of asthma co-morbidity on the susceptibility and clinical course of COVID-19 in asthma patients.
Materials and methods: Electronic databases of Pubmed and Google Scholar were searched using keyword searches.
Conclusions: Despite previous concerns about the increased risk of Covid-19 among asthmatics, most studies have not shown an increase in Covid-19 incidence among asthmatics compared to the general population.
A large number of studies that have investigate the role of concomitant asthma in the susceptibility and severity of COVID-19, show conflicting results and indicate numerous factors that may affect these processes, so there is a need for large-scale studies to adjust the result to concomitant factors, which will assess the true impact of asthma on susceptibility and severity of COVID-19.
Based on the recommendations of GINA 2020 regarding the management of asthma patients under Covid-19, potential protective effects of asthma therapy and the high risk of exacerbations when discontinuing basic therapy, we consider it appropriate to continue taking asthma patients therapy of asthma during a pandemic.

KEY WORDS: COVID-19, asthma, SARS-CoV-2, corticosteroid

INTRODUCTION

The pandemic of coronavirus disease 2019 (Covid-19), caused by a new type of coronavirus (CoV-2), associated of severe acute respiratory syndrome CoV-2 (SARS-CoV-2) is a serious challenge to the medical system of the world. According to data from the World Health Organization, as of February 25, 2021, the number of Covid-19 patients has exceeded 111 million, and the number of deaths-over 2.4 million-has continued to grow rapidly [1]. During this period, the number of Covid cases in Ukraine exceeded 1.3 million and the death toll exceeded 25,000 [2].

Asthma is one of the most common chronic respiratory diseases [3]. As we all know, the triggering factor of acute asthma attack is respiratory virus [4]. Coronaviruses are respiratory viruses and are involved in both upper respiratory tract infections and exacerbations of asthma [5]. It would be logical to assume that asthma in particular and allergies in general are risk factors for severe COVID 19, but in practice such an association has not been confirmed.

Today, there are still many unresolved questions about the combined course of asthma and Covid-19: do patients with asthma have an increased risk of onset Covid-19? Do patients with asthma have an increased risk of severe course, hospitalization, and mortality due to Covid-19? What are the pathogenetic mechanisms of asthma and Covid comorbidities? How does basic asthma treatment affect the susceptibility and course of Covid-19? In our study, we made an attempt to understand these issues.

THE AIM

The aim was to investigate the impact of asthma comorbidity on the susceptibility and clinical course of COVID-19 in asthma patients.

MATERIALS AND METHODS

The electronic databases PubMed and Google Scholar were searched by keywords: COVID-19, SARS-CoV-2, asthma, respiratory obstructive diseases. The search was limited to English-language literature. Initially, 782 publications were identified, of which 84 publications were selected for systematic analysis. The articles included in the review were published in the period from December 2019 to February 10, 2021.

REVIEW AND DISCUSSION

The prevalence of asthma among patients with Covid-19.

Literature data on the prevalence of asthma among patients with Covid-19 vary significantly depending on the country of observation. For example, according to some studies [6, 7], the prevalence of asthma among patients on Covid-19 in China in early 2020 was <1%, which is less than the prevalence of asthma in the general population of China, which is according to various sources from 1.24 up to 5.8% [8]. At the same time, studies from USA show

a significantly higher prevalence of concomitant asthma in Covid-19 – from 9 to 14.4% [9-11], which corresponds to the frequency of asthma in the general population. Data from studies on the prevalence of concomitant asthma among patients with Covid-19 are presented in Table I.

Relationship between the presence of asthma and the severity of the course, the risks of hospitalization and death in patients with Covid-19.

Conducted by Wang Y, et al. A meta-analysis of the available studies did not establish a significant difference between the incidence of concomitant asthma in patients with severe Covid-19 compared with patients with mild Covid-19 (odds ratio (OR) = 1.36, 95% confidence interval (CI): 0.79– 2.34, p = 0.27) [15]. Moreover, according to the same study, asthma was not associated with an increased risk of mortality in patients with COVID-19 (OR = 1.03, 95% CI: 0.55-1.93, p = 0.92) [15].

Concurrently, Mendy A, et al. demonstrate in their study an increased risk of hospitalization (OR: 1.92, 95% CI: 1.10-3.35, p= 0.022), admission to the intensive care unit (ICU) (OR: 4.33, 95% CI: 2.18-8.58, p < 0.001) and severe course (OR: 3.11, 95% CI: 1.67-5.80, p<0.001) Covid-19, associated with concomitant asthma [11]. Similar data were obtained by Zhu Z et al. – patients with Covid-19 with concomitant asthma, compared with patients without asthma, had a significantly higher risk of severe Covid-19 (OR 1.44; 95% CI, 1.18-1.76; p < 0.001) [16]. Detailed analysis of asthma phenotypes in the study by Zhu Z, et al. in patients with Covid-19 allowed to establish that the phenotypes of non-allergic asthma (OR: 1.48; 95% CI: 1.15-1.92; p = 0.003) and asthma in combination with chronic obstructive pulmonary disease (OR: 1.82; 95% CI: 1.16- 2.86; p = 0.009) are associated with a risk of severe Covid-19, at the same time there was no significant difference in the severity of Covid-19 depending on the presence of an allergic phenotype of asthma (p = 0.09) [16].

Mahdavinia M, et al., based on a retrospective analysis of 935 cases of Covid-19, reports a probable prolongation of the duration of mechanical ventilation of patients with severe Covid-19 with concomitant asthma compared with patients without asthma (medians 10.17 ± 6.9 and 5.28 ± 5.9 days, respectively, p = 0.002) in the group of patients aged 18-64 years [17] . However, a significant difference in the length of stay in the ventilation of patients with severe Covid-19 with concomitant asthma compared with patients without asthma in the group of patients over 65 years was not observed (medians 10.64 ± 7.38 and 8.11 ± 5.26 days, respectively, p = 0.07). Also, this study did not find a reliable relationship between the presence of concomitant asthma and higher mortality (1.1% vs. 3% in patients with asthma versus patients without asthma, p = 0.22), or with acute respiratory distress syndrome (8,9% vs. 9.5% in patients with asthma versus patients without asthma, p = 0.92) among patients with COVID-19 [17].

According to a study by Hussein MH, et al. asthma was not associated with a higher risk of admission to the ICU (OR = 1.81, 95% CI = 0.98–3.09, p = 0.06) and endotracheal intubation (OR = 1.77, 95% CI). 0.99–3.04, p = 0.06).

In addition, the presence of asthma was not associated with a greater risk of complications (OR = 1.37, 95% CI = 0.82-2.31, p = 0.23), a long period of hospital stay (OR = 1 , 48, 95% CI = 0.82-2.66, p = 0.20), as well as with the length of stay in the ICU (OR = 0.76, 95% CI = 0.28-2.02, p = 0.58) [18].

Pathogenetic aspects of the combined course of asthma and Covid-19.

CoV-2 enters the host cell through the angiotensin-converting enzyme II (ACE II) receptor. Once in the cytoplasm, CoV-2 releases genomic RNA and begins replication in the host cell. The presence of double-stranded RNA can cause an innate immune response through sensitization of the Toll-like receptor (TLR) -3, and then activation of the production of type 1 interferon (INF) [19]. Type 1 IFNs are important antiviral cytokines that can induce the expression of interferon-stimulated genes [20]. On the other hand, the adhesion protein (S-protein) of the virus can be recognized by TLR-4 and lead to the activation of pro-inflammatory cytokines, attracting lymphocytes and leukocytes to the site of infection [20]. Regarding adaptive immune responses, CoV-2 antigens are presented to T cells by antigen-presenting cells, leading to T cell activation and differentiation [19].

The interaction between the innate and adaptive immune systems is important for antiviral responses. If adaptive immune responses are insufficient to eliminate the virus, innate immune responses are likely to be hyperactivated, which can lead to uncontrolled inflammation [21]. Data from COVID-19 studies suggest a possible mechanism of cytokine storm, which is based on an increased pro-inflammatory profile of cytokines, especially in severe patients [21]. In a study by Huang, et al. studied the number of cytokines in 41 patients with COVID-19 and found that the levels of interleukin (IL) -1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, IFN-γ, IFN-γ- inducible protein, granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor, basic fibroblast growth factor, monocyte chemoattractant protein, macrophage inflammatory protein 1 alpha, macrophage inflammatory protein 1 beta, tumor necrosis factor (TNF-α), platelet-derived growth factor and vascular endothelial growth factor in patients with COVID-19 significantly higher than in healthy controls [21]. The same authors also note that patients treated in the intensive care unit had higher concentrations of IL-2, IL-7, IL-10, IFN-γ- inducible protein, granulocyte-colony stimulating factor, macrophage inflammatory protein 1 alpha, monocyte chemoattractant protein and TNF-α [21].

It is generally accepted that antiviral and allergic reactions are two separate groups of immunity and are regulated reciprocally, including an extensive network of interactions [22]. IFNs are a family of important antiviral cytokines that play a central role in this regulatory network. It has been suggested that allergic reactions to asthma patients may suppress the antiviral response, manifested as increased susceptibility and insufficient immune response to viral infection [22].

Previous studies have shown that in patients with asthma there is a decrease in the expression of IFN-α and -β epi-

Table I. The prevalence of concomitant asthma among patients with Covid-19

Authors	Country	Number of observations	Gender (men / women)	Age, years	Patients with asthma,%
Chen N et al. [6]	China	99	67/32	Mean: 55,5	1%
Li X et al. [7]	China	548	279/269	Median: 60 (48-69)	0,9%
Richardson S et al. [9]	USA	5700	3437/2263	Median: 63 (52-75)	9%
Chhiba KD et al. [10]	USA	1526	718/808	-	14,4%
Mendy A et al. [11]	USA	689	365/324	Mean: 49,5	10,24
Regina J et al. [12]	Switzerland	145	90/55	Median: 62 (52-74)	7%
Borobia AM et al. [13]	Spain	3127	1074/1152	Median: 61 (46-78)	5,2%
Shabrawishi M et al. [14]	Saudi Arabia	150	90/60	Mean: 46.1	2,7%

thelial cells of the bronchi and plasmacytoid dendritic cells (PDC) in response to viral infection, which in turn leads to increased viral load and adverse clinical consequences [23] . In addition, immunoglobulin E (IgE)-related allergic reactions can suppress antiviral immune responses by reducing the IFN-α response, reducing TLR-7 regulation, and interrupting PDC maturation [23].

It should also be noted the potential effect of eosinophils on CoV-2, which according to previous studies may be to promote viral clearance and antiviral protection of the host, although this phenomenon is not observed in all circumstances [23]. Thus, the ability of eosinophils to protect against viral infection [23] may explain the low prevalence of asthma patients among patients with COVID-19. Interestingly, some studies have shown eosinopenia in patients with COVID-19, which is more pronounced in severe patients than in lung patients [10, 5, 11]. However, whether such eosinopenia is a consequence of impaired immunity, or whether it is the result of direct targeting of viruses, remains to be seen.

The effect of asthma therapy on the course of Covid-19.
Inhaled corticosteroids
Inhaled corticosteroids (ICS), alone or in combination with bronchodilators, are recommended for daily basic treatment of asthma [3]. However, there are a number of paradoxes regarding their impact on viral infections and the frequency of exacerbations that are relevant when considering the use of ICS during a COVID-19 pandemic. In vitro studies suggest that ICS may worsen innate immune antiviral responses, and their use may lead to decreased viral clearance [24]. Conversely, there is evidence that ICS may be useful in treatment of viral infections, especially in the case of coronavirus [24]. It is important to note that most studies have been performed with rhinovirus, and the response to other viruses may be different.

There are early suggestions that ciclesonide blocks SARS-CoV-2 RNA replication in vitro and inhibits the cytopathic activity of SARS-CoV-2 [20], which may be important in reducing the risk of developing COVID-19 in response to SARS-CoV-2 infection or reducing the severity of the disease [24].

Recent studies indicate that the use of ICS inhibits the expression of the SARS-CoV-2 ACE II receptor through an interferon-dependent mechanism of type I [25]. These effects may contribute to changes in susceptibility to COVID-19 in patients receiving such therapy. There is a need for further studies to determine the exact effects that altered ACE2 expression has on susceptibility to SARS-CoV-2 infection and the comorbidity of COVID-19. There are currently two randomized trials investigating the role of ICS in people admitted to hospital with laboratory-confirmed SARS-CoV-2 infection (NCT04331054) and mild COVID-19 (NCT04330586). Therefore, the potential anti-inflammatory and antiviral effects of low-dose inhaled corticosteroids in asthma patients need further investigation.

However, there is no doubt that the systematic use of ICS reduces the frequency of exacerbations of asthma. If patients with stable asthma discontinue or reduce the dose of ICS due to concerns about their immunosuppressive effect or increased risk of developing COVID-19, they significantly increase the risk of exacerbation of asthma.
Allergen immunotherapy
Allergen immunotherapy (AIT) has been used in allergic diseases for a long time, and many new therapeutic advances have been introduced in recent years. The main mechanisms of AIT include a very early desensitizing effect, modulation of T and B cell responses, and prevention of tissue autoaggression and degranulation of allergy effector cells (mast cells, basophils, and eosinophils) [25]. An essential process of AIT is the generation and maintenance of functional allergen-specific regulatory T (Treg) cells and regulatory B (Breg) cells. Treg cells, together with their inhibitory cytokines such as IL-10 and transforming growth factor β, suppress the immune response of type 2 T-helpers and control allergic inflammation [23]. In addition, Treg cells have been shown to play a role in preventing cytokine storms and limiting tissue damage [25]. Given the putative pathomechanism of cytokine storms in critically ill patients with COVID-19, it is possible that AIT-induced immune tolerance may play a protective role. Of course, this concept is an assumption, and it requires further study.
Monoclonal antibodies against IgE
Since 2003, omalizumab, a monoclonal antibody against human IgE, has been approved for the treatment of severe, persistent asthma. As expected, recent studies have shown

that IgE blockade can reduce susceptibility to respiratory viral infection by enhancing IFN-α signaling in the PDC [23]. In the PROSE study, omalizumab treatment reduced the duration of rhinovirus infection, virus clearance, and the incidence of rhinovirus infection [23]. In addition, treatment with omalizumab reduces the level of IL-33, which induces the production of pro-inflammatory cytokines (including IL-6, IL-1β, TNF-α, MCP-1 and prostaglandin D2) [23]. Taken together, these observations suggest a potential effect of omalizumab on antiviral responses, although this area requires more detailed and extensive research.

CONCLUSIONS

Despite previous concerns about the increased risk of Covid-19 among asthmatics, most studies have not shown an increase in Covid-19 incidence among asthmatics compared to the general population.

A large number of studies that have studied the role of concomitant asthma in the susceptibility and severity of COVID-19, show conflicting results and indicate numerous factors that may affect these processes. These include the severity of asthma itself, the asthma phenotype (allergic or non-allergic), basic asthma therapy (corticosteroids or lack of corticosteroids) and other comorbidities. Due to this complex interaction between the many factors that may affect the course of Covid-19 in the context of asthma, there is a need for large-scale studies to adjust the result to concomitant factors, which will assess the true impact of asthma on susceptibility and severity of COVID-19.

Based on the recommendations of GINA 2020 regarding the management of asthma patients under Covid-19, potential protective effects of asthma therapy and the high risk of exacerbations when discontinuing basic therapy, we consider it appropriate to continue taking asthma patients therapy of asthma during a pandemic.

REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard. Available from: https://covid19.who.int
2. Coronavirus in Ukraine. https://index.minfin.com.ua/ua/reference/coronavirus/ukraine/ .
3. GINA: interim guidance about covid-19 and asthma. 2020. https://ginasthma.org.
4. Ko F.W., Chan P.K-sheung, Chan R.W. et al. Molecular detection of respiratory pathogens and typing of human rhinovirus of adults hospitalized for exacerbation of asthma and chronic obstructive pulmonary disease. Respiratory Research. 2019; 20(1). doi:10.1186/s12931-019-1181-0 .
5. Zheng X., Xu Y., Guan W., Lin L. Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review. Archives of Virology. 2018;163(4):845-53. doi:10.1007/s00705-017-3700-y.
6. Chen N., Zhou M., Dong X. et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; 395(10223):507-13. doi:10.1016/s0140-6736(20)30211-7 .
7. Li X., Xu S., Yu M. et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology. 2020;146(1):110-18. doi:10.1016/j.jaci.2020.04.006.
8. Huang K., Yang T., Xu J. et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394(10196):407-418. doi:10.1016/S0140-6736(19)31147-X.
9. Richardson S., Hirsch J.S., Narasimhan M. et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052. doi:10.1001/jama.2020.6775.
10. Chhiba K.D., Patel G.B., Vu T.H. et al. Prevalence and characterization of asthma in hospitalized and nonhospitalized patients with COVID-19. Journal of Allergy and Clinical Immunology. 2020;146(2). doi:10.1016/j.jaci.2020.06.010 .
11. Mendy A., Apewokin S., Wells A.A., Morrow A.L. Factors Associated with Hospitalization and Disease Severity in a Racially and Ethnically Diverse Population of COVID-19 Patients. 2020. doi:10.1101/2020.06.25.20137323.
12. Regina J., Papadimitriou-Olivgeris M., Burger R. et al. Epidemiology, Risk Factors and Clinical Course of SARS-CoV-2 Infected Patients in a Swiss University Hospital: An Observational Retrospective Study. SSRN Electronic Journal. 2020. doi:10.2139/ssrn.3578783.
13. Borobia A.M., Carcas A.J., Arnalich F. et al. A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe. J Clin Med. 2020;9(6):1733. doi:10.3390/jcm9061733.
14. Shabrawishi M., Al-Gethamy M.M., Naser A.Y. et al. Clinical, radiological and therapeutic characteristics of patients with COVID-19 in Saudi Arabia. PLoS One. 2020;15(8):e0237130. doi:10.1371/journal.pone.0237130.
15. Wang Y., Ao G., Qi X., Xie B. The association between COVID-19 and asthma: A systematic review and meta-analysis. Clin Exp Allergy. 2020;50(11):1274-77. doi:10.1111/cea.13733.
16. Zhu Z., Hasegawa K., Ma B. et al. Association of asthma and its genetic predisposition with the risk of severe COVID-19. J Allergy Clin Immunol. 2020;146(2):327-29.e4. doi: 10.1016/j.jaci.2020.06.001.
17. Mahdavinia M., Foster K.J., Jauregui E. et al. Asthma prolongs intubation in COVID-19. J Allergy Clin Immunol Pract. 2020;8(7):2388-91. doi:10.1016/j.jaip.2020.05.006.
18. Hussein M.H., Toraih E.A., Attia A.S. et al. Asthma in COVID-19 patients: An extra chain fitting around the neck? Respir Med. 2020;175:106205. doi: 10.1016/j.rmed.2020.106205.
19. Li G., Fan Y., Lai Y. et al. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424-32. doi: 10.1002/jmv.25685.
20. de Wilde A.H., Snijder E.J., Kikkert M., van Hemert M.J. Host Factors in Coronavirus Replication. Curr Top Microbiol Immunol. 2018;419:1-42. doi:10.1007/82_2017_25.
21. Zhang W., Zhao Y., Zhang F. et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin Immunol. 2020 May;214:108393. doi: 10.1016/j.clim.2020.108393.
22. Gonzales-van Horn S.R., Farrar J.D. Interferon at the crossroads of allergy and viral infections. J Leukoc Biol. 2015;98(2):185-94. doi:10.1189/jlb.3RU0315-099R.
23. Liu S., Zhi Y., Ying S. COVID-19 and Asthma: Reflection During the Pandemic. Clin Rev Allergy Immunol. 2020;59(1):78-88. doi:10.1007/s12016-020-08797-3.
24. Halpin D.M.G., Singh D., Hadfield R.M. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J. 2020;55(5):2001009. doi:10.1183/13993003.01009-2020.

25. Schultze A., Walker A.J., MacKenna B. et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. Lancet Respir Med. 2020;8(11):1106-20. doi:10.1016/S2213-2600(20)30415-X.

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