Are patients with lung cystic fibrosis at increased risk of severe and fatal COVID-19? Interleukin 6 as a predictor of COVID-19 outcomes

To the editor The recently published review by Kosmaczewska and Frydecka[1] prompted us to investigate how the dysregulation of the immune system during coronavirus disease 2019 (COVID-19) might affect patients with concomitant chronic pulmonary diseases. Herein, we present our novel hypothesis relevant to the pathogenesis of cytokine storm in COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily targets the lungs and results in pneumonia and acute respiratory distress syndrome. Therefore, patients with pre-existing pulmonary diseases are more likely to develop severe symptoms of infection. Surprisingly, recent epidemiological data have shown that comorbid chronic respiratory conditions do not represent major risk factors in patients with COVID-19. Cystic fibrosis (CF) is an interesting example. There is emerging evidence indicating that the severity of SARS-CoV-2 infection in CF is milder than predicted, even though CF is frequently associated with diabetes, a strong predictor of severe course of SARS-CoV-2 infection.[2] Furthermore, patients with CF are at increased risk of severe infection with other viruses affecting the respiratory system. Influenza viruses, the H1N1 virus in particular, have been shown to cause disease progression in lung CF. Therefore, many countries categorized people with CF as highly vulnerable to COVID-19 and advised them to stay at home in order to minimize the risk of contracting the virus.[3]

The fatal outcome of COVID-19 is associated with cytokine storm and acute respiratory distress syndrome. Interleukin 6 (IL-6) is considered the key cytokine in the pathogenesis of cytokine storm. Remarkably, in most studies, IL-6 levels are reported to be increased in severe COVID-19, and elevated IL-6 levels have been associated with higher mortality.[4]

We hypothesize that constitutively low levels of IL-6 present in the inflamed airway tract of patients with CF may contribute to inhibiting the cytokine storm associated with severe SARS-CoV-2 infection and, hence, limit the severity of the infection in this population. We examined a group of 39 patients with advanced lung CF and confirmed chronic *Pseudomonas aeruginosa* infection. The patients' sputa contained an unusual combination of high proinflammatory IL-8 levels (median, 1178 pg/ml) accompanied by the extremely low levels of proinflammatory cytokine IL-6 (median, 243 pg/ml) and the anti-inflammatory cytokine IL-10 (median, 196 pg/ml). Low sputum IL-6 levels were also associated with high tumor necrosis factor α levels in an independent study of patients with CF. Importantly, IL-6 suppression was limited to the sputum, while systemic IL-6 production was normal.[5] This phenomenon is not observed in other chronic inflammatory pulmonary diseases.

The mechanism of suppressed IL-6 production in the airways of patients with CF remains unclear. However, these observations have relevant implications for the treatment of SARS-CoV-2. The association between the localized suppression of IL-6 in the airways of patients with CF and decreased SARS-CoV-2 infection morbidity provides strong support for targeting IL-6 production or IL-6 receptor blockade in patients with COVID-19. Furthermore, the localized cytokine imbalance in patients with CF highlights the role of monitoring local (sputum) cytokine levels during any therapeutic intervention.

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Authors' reply We would like to thank Prof. Marcinkiewicz and his colleagues for their interest in our review describing the impact of the pre-existing immune status on the clinical course of COVID-19.[1] We appreciate the information added in their letter to the editor,[2] reporting their own data suggesting that the immune alterations observed in patients with lung cystic fibrosis (CF) might protect against severe COVID-19 due to the low airway level of IL-6, a cytokine considered an immunological predictor of disease severity. The authors provided support for targeting IL-6 in COVID-19, hence emphasizing the major role of pre-existing immune system dysregulation for the clinical outcome of SARS-CoV-2 infection. They paid special attention to chronic pulmonary diseases being other possible risk factors for SARS-CoV-2 infection. In this reply, we suggest that immune imbalance related to allergic asthma and therapeutics controlling the disease severity may protect asthmatic patients against severe COVID-19.

Allergic and antiviral responses are reciprocally regulated, hence indicating higher susceptibility of asthmatic individuals to infections caused by viruses affecting the respiratory system. In fact, the deficient antiviral response associated with impaired interferon production by bronchial epithelial cells and plasmacytoid dendritic cells in patients with allergic asthma makes them prone to viral infections.[3] Therefore, concomitant asthma should be expected to be a strong risk factor for worse clinical outcomes in COVID-19. Although studies have reported various prevalence rates regarding asthma in patients with COVID-19 compared with the general adult population, its frequency remains significantly lower than expected from previous experience with other respiratory diseases. Moreover, asthmatic patients with SARS-CoV-2 infection most frequently exhibit no symptoms or develop mild disease; death is rare and most often associated with oral corticosteroid administration prior to intensive care unit admission.[3] Furthermore, the coexistence of asthma and SARS-CoV-2 infection does not affect the clinical course of COVID-19 regardless of high-risk comorbidities (ie, age, obesity, hypertension, diabetes, and hyperlipidemia) or use of asthma control medication.[3,4]

The relatively low number of asthmatics among patients with COVID-19 may result from skewing the immune balance towards the type 2 response, including the induction of T helper cells, type 2 B cells, M2 macrophages, group 2 innate lymphoid cells, eosinophils, and mast cells.[3] As a consequence, immune and epithelial cells produce a variety of cytokines that develop an asthma-mediated regulatory network, such as IL-4, IL-5, IL-13, and IL-33. They exert an anti-inflammatory effect by dampening the type 1 proinflammatory response, including the production of IL-1β, IL-6, tumor necrosis factor α, and other inflammatory chemokines. Therefore, it is highly probable that the asthma-signature type 2 response counteracts the proinflammatory cytokine action involved in the pathogenesis of COVID-19, hence alleviating the severity of SARS-CoV-2 infection. By promoting viral clearance and antiviral host defense, the increased number of eosinophils (considered a cell signature of atopic asthma) may account for the relatively low number of asthmatics among patients with COVID-19, in accordance with the finding that severe eosinopenia is clearly correlated with worse COVID-19 prognosis.[3]

Also, asthma control based on therapeutics affecting the immune response, including low-dose inhaled corticosteroids, allergen immunotherapy, and biologic treatment with monoclonal antibodies such as mepolizumab, benralizumab, and omalizumab (anti-IL-5, IL-5Rα, and anti-IgE monoclonal antibodies, respectively, registered in Poland), cannot be underestimated in mitigating the risk of SARS-CoV-2 infection. They can dampen proinflammatory cytokines and enhance the antiviral response with interferons signaling reinforcement.[3,5] Furthermore, inhaled corticosteroids are associated with reduction in angiotensin-converting enzyme 2 and transmembrane protease serine 2 enzyme gene expression and suppressed replication of other coronaviruses, suggesting their possible involvement in protection against SARS-CoV-2 infection in patients with allergic asthma.[5] Allergen immunotherapy may trigger immune tolerance through generation and maintenance of functional regulatory T and B cells involved in the prevention of cytokine storm. In turn, administration of biologic therapeutics, limited to severe cases of asthma not controlled adequately with other treatments, allows for reduced systemic steroid use and, thus, lowers the risk of developing critical COVID-19.[3,5]

Apart from the nonsevere course of COVID-19 in asthmatic patients, lack of asthma exacerbation

during SARS-CoV-2 infection also supports the hypothesis that sufficiently controlled asthma-related alterations in the immune system might improve clinical outcomes in COVID-19.[3] Furthermore, the observation that a mild course or easily controlled atopic disease corresponds with a normal antiviral interferon response strengthens the significance of controlling disease activity.[3] Controlling asthma and preventing its exacerbation are also necessary to avoid hospitalization and oral corticosteroid use, which represent risk factors for in-hospital exposure to SARS-CoV-2 and development of COVID-19.[5]

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