POLISH ARCHIVES OF
Internal Medicine
POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ

ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formated version will be made available soon.

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

Authors: Janusz Marcinkiewicz, Henryk Mazurek, Grzegorz Majka, Benjamin Chain

Article type: Letter to the Editor

Received: October 2, 2020.

Accepted: October 5, 2020.

Published online: October 5, 2020.

ISSN: 1897-9483

Title: *Are patients with lung cystic fibrosis at increased risk for severe and fatal COVID-19? Interleukin-6 as a predictor of COVID-19 outcome*

Authors: Janusz Marcinkiewicz[1], Henryk Mazurek[2], Grzegorz Majka[1] and Benjamin Chain[3]

[1]Jagiellonian University Medical College, Faculty of Medicine, Chair of Immunology, Czysta 18, 31-121 Kraków, Poland

[2]Department of Pneumonology and Cystic Fibrosis, Institute of Tuberculosis and Lung Disorders, Rabka-Zdrój, Poland

[3]Division of Infection & Immunity, University College London, UCL Cruciform Building, Gower Street, London, United Kingdom

Short title: *Impact of IL-6 on COVID-19 outcome in cystic fibrosis patients.*

Corresponding author: Janusz Marcinkiewicz, Prof., Jagiellonian University Medical College, Faculty of Medicine, Chair of Immunology, Czysta 18, 31-121 Kraków, Poland, e-mail: janusz.marcinkiewicz@uj.edu.pl, phone: 00 48 12 632 58 65

Declaration of interests

JM, HM and GM acknowledge the support from the research grant from National Science Centre, Poland.

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

The recently published report by Kosmaczewska and Frydecka [1] prompted us to consider how dysregulation of the immune system during COVID-19 might affect the patients with coexisting chronic pulmonary diseases. Herein, we present our novel hypothesis relevant to pathogenesis of cytokine storm in COVID-19.

Sars-CoV-2 (severe acute respiratory syndrome coronavirus) primarily targets the lungs resulting in pneumonia and acute respiratory distress syndrome (ARDS). Therefore, it is more likely to develop severe symptoms if patients have pre-existing lung problems Surprisingly, recent epidemiological data show that comorbid chronic respiratory conditions are not major risk factors in patients with COVID-19. An interesting example is cystic fibrosis (CF) where there is emerging evidence that severity of Sars-CoV-2 infection is milder than predicted, even though CF is frequently associated with diabetes, a strong predictor of severe Sars-CoV-2 disease.[2] Furthermore, CF patients are at enhanced risk of severe infection with other respiratory viruses. Influenza viruses, the H1N1 pandemic in particular, have been shown to cause disease progression in CF lung disease. Therefore, many countries have categorised people with CF as highly vulnerable to COVID-19 infections and have advised them to stay at home to minimise the risk of contracting the virus.[3]

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

We propose that constitutively low levels of IL-6 present in the inflamed airway tract of CF patients may contribute to inhibiting the cytokine storm associated with severe Sars-CoV-2 and hence limit the severity of the infection in these individuals. We investigated a group of 39 patients with advanced CF lung disease and confirmed chronic *P. aeruginosa* infection, and found that their sputa contained an unusual combination of high levels of pro-inflammatory IL-8 (median of 1178 pg/ml), associated with extremely low levels of the pro-inflammatory cytokine IL-6 (median of 243 pg/ml) and the anti-inflammatory cytokine IL-10 (median of 196 pg/ml) in sputum. Low sputum IL-6 levels were also associated with high

TNF-alpha in an independent study of CF patients Importantly, IL-6 suppression was localised to sputum measurements, while systemic IL-6 production was normal.[5] This phenomenon is not observed in other chronic inflammatory lung diseases.

The mechanism of suppressed IL-6 production in airways of CF patients is unresolved. However, these observations have important implications for treatment of Sars-CoV-2. The association between localised suppression of IL-6 in the airways of CF patients and decreased Sars-CoV-2 morbidity provide strong support for targeting IL-6 production or IL-6 receptor blockade in COVID-19 patients. Furthermore, the localized cytokine imbalance in CF patients highlight the importance of monitoring local (sputum) cytokine levels during any therapeutic intervention.

Acknowledgments

This work was supported by the study conducted during the research project granted to JM (project number 2017/27/B/NZ6/001772) financed by the National Science Centre, Poland.

References

1. Kosmaczewska A, Frydecka I. Dysregulation of the immune system as a driver of the critical course of the novel coronavirus disease 2019. Pol Arch Intern Med. 2020; 130: 779-788.
2. Colombo C, Burgel P-R, Gartner S et al. Impact of COVID-19 on people with cystic fibrosis. Lancet Respir Med. 2020; 8: e35-e36.
3. Cosgriff R, Ahern S, Bell SC et al. A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis. J Cyst Fibros. 2020; 19: 355-358.
4. Han H, Ma Q, Li C et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerging Microbes Infect. 2020; 9: 1123-1130.
5. Osika E, Cavaillon J, Chadelat K et al. Distinct sputum cytokine profiles in cystic fibrosis and other chronic inflammatory airway disease. Eur Respir J. 1999; 14: 339-346.