IMMUNE RESPONSE TO COVID-19 COMPARED TO THE IMMUNE RESPONSE TO SARS, MERS AND INFLUENZA

Velo Markovski

Faculty of Medical Sciences, Goce Delchev University, Shtip, North Macedonia

ABSTRACT

The course, form and outcome of an acute respiratory illness, as well as its patho-histological features largely depend on the level of inflammatory cytokines. The most important proinflammatory cytokines and chemokines are: IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17A, IFN-γ, TNF-α and GM-CSF. There are many similarities in the human immune response to influenza, SARS and MERS-CoV. Available studies of COVID-19 show a completely different immune response, i.e. immunological indifference or suppression.

Influenza is a disease we have known for a long time. WHO has been successfully following the antigenic drift of influenza virus ever since 1952 (WHO's Global Influenza Surveillance and Response System (GISRS). This is necessary to monitor epidemiological characteristics of influenza as well as for the components of the seasonal vaccine which contains the antigenic characteristics of the subtypes and variants of influenza A virus that circulated in the previous season in the southern hemisphere. Throughout this period, many viruses and bacteria caused respiratory infections, sometimes in increasing epidemic numbers, but it was only the flu that caused serious problems. The epidemics were accompanied by high morbidity and significant mortality. Beta-corona viruses caused a serious warning in 2002 when SARS Cov-1 and MERS in 2012 appeared, followed by high mortality. Alpha corona viruses have been present all this time, but have caused mild upper respiratory infections and rhinitis, without serious consequences. Depending on the season and the region, corona viruses have been present in 10 to 35% of respiratory infections with the immune response to any infectious agent, may be mild, moderate and consequently heal, or severe when due to the high level of cytokines many barriers and membranes can be damaged and cause death. In influenza, the immune response is adequate. Only in a small percentage of cases, an overactive immune response is observed that causes damage and even death. SARS and MERS-CoV have been also shown to elicit a strong immune response.

COVID-19 has been present for only a few months, and despite the efforts of many scientists, the epidemiological characteristics and pathogenesis of the disease are still not completely clear. Although COVID-19 belongs to beta corona viruses along with SARS and MERS-CoV, there are differences in the immune response. Whether COVID-19 weakens the immune system, or the immune system does not recognize it as a serious threat, there is a weak immune response during this infection. Such a significant discrepancy in the immune response can help understand the pathogenesis of COVID 19 and the causes of primary viral pneumonia and ARDS followed by high mortality.

Keywords: *COVID-19, immune response, SARS, MERS, Influenza*

ADDRESS FOR CORRESPONDENCE:
Velo Markovski, PhD, associate professor,
specialist of Infectology
velomarko@yahoo.com
Tel. 00389 76200406

INTRODUCTION

The purpose of the present paper was to analyze the differences in the immune response between influenza, SARS and MERS-CoV on the one hand and COVID-19 - on the other, and to explain the possible causes of mortality in COVID-19. Papers from highly rated scientific journals, monographs and textbooks were reviewed to analyze the immune response to influenza during epidemics and pandemics, and to compare it to the immune response observed during corona infections.

Flu is caused by influenza types A and B, while influenza type C causes mild upper respiratory infections. Until now, pandemics have only been caused by influenza type A, with subtypes H1, H2 and H3. During a flu epidemic, caused either by influenza virus type A or B, a clinical picture with severe symptoms of general infectious syndrome always develops. In infectious diseases, viral or bacterial, the symptoms of the general infectious syndrome appear due to the cytokine response. The severity of these symptoms, such as fever, malaise, headache, bone and muscle pain, drowsiness, sore throat, etc. depend on the levels of cytokines and other elements of the immune system that modulate the immune response. During influenza infection, there is secretion of the interferon-α (IFN-α), tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) α and β, interleukin-6 (IL-6), interleukin-8 (IL-8) and

monocyte-attracting chemokines (2, 7,12, 13, 14, 15, 18, 22). A higher level of released cytokines has been accompanied by more pronounced symptoms of the general infectious syndrome. The human immune system senses the influenza virus as a serious threat and is activated immediately after the virus enters the respiratory epithelium cells. As a result of the rising cytokine levels preceeding the death of the respiratory epithelium cells the clinical picture of flu is observed, whereby after an incubation of 1-2 days the symptoms of general infectious syndrome appear. Symptoms due to the death of a large number of upper respiratory tract epithelial cells occur two to three days after the onset of the disease, such as sneezing, coughing, runny nose, and lacrimation. The latter are present for a long time after the symptoms of the general infectious syndrome have subsided. The temperature normalizes 4-5 days after the onset of the disease, as well as the other symptoms of the general infectious syndrome, as a result of the normalization of the cytokine values and other elements of the inflammatory response of the humoral and cellular immunity. The symptoms caused by the death of the respiratory epithelium cells (sneezing, coughing, runny nose) remain present until those cells are restored (2, 14, 15, 16, 22). But in a small number of people (0.01–0.02% of patients), the immune system reacts too strongly, secreting very high doses of cytokines, leading to a violent immune response that damages the barriers and membranes in the body. The most severe condition is encephalopathy, which is associated with increased levels of numerous cytokines, but in particular, with an increase in IL-6 levels. When the blood concentration of IL-6 is between 80 to 150 pg / ml there is no risk of brain dysfunction. Above 150 pg / ml a mild brain dysfunction occurs. When the level of IL-6 exceeds 6000 pg / mL, the hematoencephalic barrier is damaged, and blood elements such as bilirubin, urea, and creatinine that are toxic to neurons come into contact with CNS cells. Due to the death of CNS cells, he clinical picture of encephalopathy develops. Encephalopathies are severe conditions ending up in 30 to 50% mortality. Encephalopathies with IL6 values above 15 000 pg / mL always end in death. In addition, the impaired hematoencephalic barrier during influenza viral infection, is associated with significantly increased rates of purulent meningitis (7,16,19,20) .

Numerous studies have analyzed episodes of beta corona virus infections and the occurrence of SARS-CoV in 2002, and the 2012 Mers-CoV Middle East Respiratory Syndrome. (1, 6, 18, 25, 26, 27) In both cases, a strong immune response and a cytokine storm with an increase in IL-8, IL-1β, IL-1b and IL-6 were observed. IL-8 appears to be the major cytokine responsible for the inflammatory response in the lungs accompanied by infiltration of neutrophils, monocytes, and NK cells. Experiments in mice in which IFN- α, CCL2, IL-6, TNF- α, and IFN-γ had been induced, demonstrated inflammatory infiltrates with numerous neutrophils, monocytes, and NK cells. IL-1β was associated with tissue damage, neutrophil infiltration, acute inflammatory reactions, and severe respiratory viral infection.

From the numerous papers on COVID-19 available until now, it is evident that there is no strong immune response to this infection **(Table 1).** Leukopenia or normal leukocyte counts are present in most of the cases. The frequently observed lymphopenia is somewhat surprising. Procalcitonin level is normal. CRP increase is detected in a small percentage of cases. (1, 3, 4, 5, 12, 17,18, 22-24, 26, 27). Chuan Chin (9) analyzed the immune characteristics in a group with 452 patients with COVID-19, of which 286 were with severe infection, and 168 - with a mild clinical form. There was a slight increase in IL-6 values only to 13.3 pg / ml in patients with a mild clinical picture, as opposed to 25.2 pg / ml in severe cases (normal values 0.0–7.0 pg / mL). The other tested cytokines, IL -2R, IL-8, IL-10, and TNF-α as well as serum IgM, IgG, and IgA were within the normal ranges in both groups. The absolute numbers of helper (CD3 + CD4 +) and suppressor T cells (CD3 + CD8 +) in patients with COVID-19 were below the normal values. The decrease of helper T cells in the group with severe infection was more pronounced. The function of CD4+, CD8+ T cells, and NK cells (in terms of IFN-γ expression) were in normal ranges and no significant difference was established between severe and non-severe cases. Lymphocyte subsets were analyzed in 44 patients with COVID-19 on admission. The total number of lymphocytes: B cells, T cells, and NK cells was significantly lower in patients with COVID-19 (mean values of 852.9 cells/μL, and even lower) in severe cases, (743.6 vs. 1020) in the non-severe group. Similar results were also obtained by Yishan (22) who analyzed 125 patients, 103 of whom had COVID-19 and 22 non-COVID-19 pneumonia. Wei-jie Guan's analysis of 1,099 patients concluded that there was a difference in the clinical picture and immune response between COVID-19 and other acute respiratory infections (influenza, SARS CoV-1, MERS Cov (19). Other authors (4, 6, 18, 26) also found that the values of interleukins and other cytokines in COVID-19 were either unchanged or slightly elevated. Leukopenia and lymphopenia were present. The fact that there

is no strong immune response during COVID-19 upper respiratory tract infection is in favour of the mild clinical picture whereby the symptoms of the general infectious syndrome are either absent or of low intensity. By the second week of April, more than 2,350,000 SARS-CoV-2 positive patients have been registered worldwide, over 162,000 of whom have died. So far, not a single case of COVID-19 who has died from encephalopathy has been described. This fact is also in favour of the absence of strong immune response, or cytokine storm in SARS-CoV-2 infection.

Table 1. Cytokine levels registered in hospitalized patients during COVID-19 pandemic

author	Reference N	Number of Patients tested	TNF-α (pg/mL)	IFN-γ (pg/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-10 (pg/mL)
Chuan Qin	6	452	8.6 (6.9–10.9)		21 (6.1–47.2)	16.7 (10.2–27.0)	5.4 (5.0–9.7)
Fei Zhou	27	191			7.4 (5.3–10.8)		
Nanshan Chen	4	99			7.9 (6.1–10.6)		
Huan Han	10	102	3-64	1-8	4-32 64-250 (6 patients)	4-16 16 - 64 (7 patients)	

Cytokine storm is the term for a dramatic increase in cytokine concentrations. Cytokine storm occurs at concentrations greater than 4.000 pg/ml for NF-α, IFN-γ, IL 1, and IL 8, greater than 3.000 pg/ml for IL2 and IL 6, more than 2.000 pg/ml for IL 4, more than 1.500 pg/ml for IL 10 and more than 400 pg/ml for IL-12 (9, 10)

Based on previous experience with respiratory infections, the absence of strong immune response may be due to several reasons. The first possible option is that the respective causal agent is part of the normal microflora of the upper respiratory tract and the immune system does not recognize it as a foreign antigen and a danger to the body. The second option is the existence of specific secretory IgA. After an acute respiratory infection, in addition to IgM and IgG antibodies, the level of IgA secretory antibodies increases. These virus-specific IgA antibodies, in the case of COVID-19, neutralize the virus before it enters the cells of the respiratory epithelium, preventing the infection, so that viral antigens do not come into contact with the human immune system at all. It is possible that we currently have a second wave of COVID-19. IgG antibodies to COVID-19 are found in about ten percent of the population. A third option is the existence of cross-immunity so that antibodies to alpha corona viruses (causing seasonal infections in humans) neutralize SARS CoV-2 as well. The fourth possible explanation for the lack of a strong reaction (and absence of general infectious syndrome) is the nature of the virus itself, which manages to avoid the initial strong immune response, , as is the case with HIV infection for example. The virus itself does not cause much damage when entering the body, so there is no proper immune response. HIV enters the body without much resistance, after which it multiplies in the cells of the immune system (CD4 T lymphocytes). Indeed, in the case of SARS-CoV-2, it is paradoxical to reach a state of leukopenia lymphopenia, a decrease in T lymphocytes, for a short period of several days, in an acute infection with short incubation of about 4 (2 -14) days).

Regarding the occurrence of primary viral pneumonia, there is a large difference in the clinical manifestations of epidemic vs. pandemic influenza. During epidemics lower respiratory infections and primary influenza pneumonia are not typically observed. In general, pneumonia during influenza epidemics is due to a secondary bacterial infection. Outbreaks in inter-pandemic period are caused by small drifts in the antigenic structure of viral hemagglutinin. When the new variant appears, memory B lymphocytes recognize a similar antigen, followed by a rapid rise in antibody titters from the corresponding clone. At the same time, there is a complete immune response to the new antigenic influenza virus variant. But partial cross-action is enough to slow the spread of the influenza virus to the lower respiratory tract. When a large antigenic shift occurs and a new subtype of influenza A virus appears in the circulation, there is a lack of cross-immunity help, permitting the new subtype to descend in the lower respiratory system and cause primary viral pneumonia. In addition, during the first encounter with the new subtype of influenza A virus, a significant number of people have a very strong immune response and secretion of large amounts of

cytokines. These primary influenza pneumonias are the cause of high mortality during pandemics. (16, 19, 20) Unlike pandemic influenza viruses, COVID-19 in a large percentage of patients (about 20%) causes primary viral pneumonia. It is also very unusual that a pathogen that is not extremely virulent (has not yet been shown to have a direct cytopathogenic effect) is able to cause massive bilateral pneumonia. The second paradox is that patients with uncompromised immune system have no problem recovering from this massive viral pneumonia. (4, 5, 8, 27) This is contrary to previous experience in science, where primary viral pneumonias are accompanied by high mortality. On the average, COVID-19 pneumonia occurs 18 days after the infection, when the virus is no longer present in the body. in contrast to primary viral pneumonia presenting during the acute phase of pandemic influenza There is a rich finding on X-rays, but no enlarged lymph nodes in the mediastinum (4.8). Although there is evidence of pneumonia, very few inflammatory cells are detected in the autopsy. All this data require consideration and analysis of another possible condition or co-infection in the settings of COVID-19.

Conclusions

The host's immune response to influenza virus is strong, sometimes even excessive.

The host's immune response during SARS and MERS is strong.

Although it is a similar upper respiratory infection, the immune response in COVID-19 is weak, and in some patients it is even suppressed.

Although SARS-CoV-2 does not stimulate the immune response, it does manage to cause primary viral pneumonia in 20% of those infected.

Patients with well-functioning immune system are (paradoxically) easily cured from massive bilateral COVID-19 pneumonia.

Co-infection with another infectious agent or other condition might be the cause of COVID-19 pneumonia.

References

1. Alosaimi B, Hamed ME, Naeem A, et al. *MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower respiratory tract*. Cytokine. 2020.doi: 10.1016/j.cyto.2019.154895.
2. Aiba H, Mochizuki M, Kimura M, Hojo H. *Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy* Neurology 2001 Jul 24; 57(2):295-9.
3. Huang C, Wang Y, Li X, et al: *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China*, The Lancet, vol395, ISSUE 10223, P497-506, Feb. 15, 2020.
4. 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* Lancet. 2020 Feb 15;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7
5. Drosten C, Stephan Günther S, Wolfgang Preiser W, et al: *Identification of a novel coronavirus in patients with severe acute respiratory syndrome***,** N Engl J Med. 2003 May 15;348(20):1967-76. Epub 2003
6. Qin C, Zhou L , Hu Z, , Zhang S, , *Dysregulation of immune response in patients with COVID-19 in Wuhan, Chin,: Clinical Infectious Diseases*, 12 March 2020, https:// doi.org/10.1093/cid/ciaa248
7. Hayden F G, Strober W, Straus S E, *Local and systemic cytokine responses during experimental human influenza A virus infection, Relation to symptom formation and host defense.* J Clin Invest.;101(3):643-649,1998. https://doi.org/10.1172/JCI1355.
8. Shi H, Han X, Jiang N, Cao Y, et al.: *Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study* The Lancet Infectious Diseases 20(4), P425-434,2020, DOI: 10.1016/S1473-3099(20)30086-4
9. Yiu HH, Graham AL, Stengel RF: *Dynamics of a Cytokine Storm*, Plose One, 2012, https://doi.org/10.1371/journal.pone.0045027
10. 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 & Infections, 9:1, 1123-1130, may 2020, DOI: 10.1080/22221751.2020.1770129
11. Kim HO, Kim HS, Youn JC, Shin EC and Park S: *Serum cytokine profiles in healthy young and elderly population assessed using multiplexed bead-based immunoassays*, Journal of Translational Medicine 2011, 9:113, http://www.translational-medicine.com/content/9/1/11
12. Junttila IS: *Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes* Front, Immunol., 07 June 2018, https://doi.org/10.3389/fimmu.2018.00888
13. Teijaro JR, Walsh KB, , Cahalan S, et al. *Endothelial Cells Are Central Orchestrators of Cytokine Amplification during Influenza Virus Infection*, Cell. 2011 Sep 16;146(6):980-91. doi: 10.1016/j.cell.2011.08.015
14. La Gruta, N.L., Kedzierska, K., Stambas, J., and Doherty, P.C. *A question of self-preservation: immunopathology in influenza virus infection.* Immunol. Cell Biol. 2007, 85, 85–92.
15. Van Reeth K: *Cytokines in the pathogenesis of influenza*, Veterinary, 2000 74,(1–2**)**,: 109-116, https://doi.org/10.1016/S0378-1135(00)00171-1G
16. Markovski, V : *Influenza: Epidemics and pandemics*, LAP LAMBERT Academic Publishing, 2013. dp/365949478X
17. Ridker PM: *Targeting Interleukin Signaling Pathways for the Treatment of Atherothrombosis Circulation Research* 2019,124, (3):437-450 https://doi.org/10. 1161/CIRCRESAHA.118.313129
18. Mehta P, Daniel, F Mc Aulej et al.:*COVID-19: consider cytokine storm syndromes and immunosuppression* The Lancet, Volume 395,ISSUE 102229,P1033-34,2020, https://doi.org/10.1016/ S0140-6736(20)30628-0
19. Surtees R and De Sousa: *Influenza virus associated encephalopathy* Arch Dis Child. 2006 Jun; 91(6): 455 456.doi: 10.1136/adc.2005.092890
20. Ichiyama T, Kimura , M Shibata , Ishiwada N et al.: *Detection of influenza virus RNA by reverse transcription-PCR and proinflammatory cytokines in influenza-virus-associated encephalopathy*, Jour. Med. Immunology, Volume 58, Issue4, Pages 420-425, August 1999 https://doi.org/10.1002/(SICI)1096-9071(199908)58:4<420:AID-JMV16>3.0.CO;2-T
21. Walsh KB, Teijaro JR, Wilker PR, Jatzek A, et al*., Suppression of cytokine storm with a sphingosine analogy provides protection against pathogenic influenza viru*s. Proc Natl Acad Sci U S A. 2011 Jul 19;108(29):12018-23. doi: 10.1073/pnas.1107024108. Epub 2011 Jun 29.
22. Wei-jie Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, et al.: Clinical *Characteristics of Coronavirus Disease 2019 in China*, *The* New England journal *of* medicine February 28, 2020,*DOI: 10.1056/NEJMoa2002032*
23. WHO: Q&A on coronaviruses (COVID-19), 8 April 2020 (https://www.who.int/news-room/q-a-detail/ q-a-coronaviruses)
24. Xuetao Cao: *COVID-19: immunopathology and its implications for therapy*, Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-0308-3
25. Zheng Y, Huang Z, Ying G, Zhang X, Ye W, Hu Z: *Study of the lymphocyte change between COVID-19 and non-COVID-19 pneumonia cases suggesting other factors besides uncontrolled inflammation contributed to multi-organ injury,* The Lancet Respiratory Medicine,2020, http://dx.doi.org/10.2139/ssrn.3555267
26. Y Shi Y, Wang Y, Shao C, et al: *COVID-19 infection: the perspectives on immune responses*, Cell Death & Differentiation, 2020, https://doi.org/10.1038/s41418-020-0530-3
27. Zhou F, Yu T, Du R, et al,: *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet. 2020 Mar 28; 395 (10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3.