PROF. MILOS JESENAK (Orcid ID : 0000-0001-7976-2523)

Article type : Letter to the Editor

COVID-19, chronic inflammatory respiratory diseases and eosinophils –
Observationsfrom reported clinical case series

To the Editor,

Currently, the world is facinga global pandemicwith a new coronavirus SARS-CoV- 2 (**S**evere **A**cute **R**espiratory **S**yndrome **Co**rona**V**irus Type **2**) causing infectious disease named COVID-19 (**Co**rona**V**irus **I**nfectious Disease 20**19**). Comparing the clinical presentation and epidemiological characteristics of COVID-19 with previous coronavirus-associated respiratory diseases (SARS-CoV1 and MERS) revealedsome remarkable findings and differences. Moreover, the clinical course of SARS-CoV-2 infection showed the complexity of COVID-19 profile with the variable clinical presentations [1]. Recently published clinical reports tried to identify possible risk factors resulting ina higher incidence of COVID-19 infection associated with complications and a severe disease. It seems that elderly people and/or immune-compromisedindividuals are at the highest riskwhile males showed higher mortality rate [2].Other important risk factors include various comorbidities affecting 34.9 to79.3% of COVID-19 patients[3,4]. Several authors observed that the severity of its clinical manifestation is associated with certain individual characteristics of the infected patients. In general, pre-existing chronic respiratory conditions (including bronchial asthma, COPD, bronchiectasis) are reported only in a small proportion of patients [3,5-8]. This is in contrast with the other respiratory viral infections(e.g. influenza, rhinovirus), which are typically affecting allergic patients and those with chronic respiratory diseases. In a group of 140 patients from Wuhan (China), comorbidities were noted in 79.3% of

severe patients (hypertension in 37.9%; diabetes mellitus in 13.8%; liver diseases in 6.9%; coronary heart diseases in 6.9%; COPD in 3.4%) and in 53.7% of non-severe patients (hypertension in 24.4%; diabetes mellitus in 11.0%; liver disease in 5.0%; coronary heart diseases in 3.7%; COPD in 0%)[4]. Other chronic diseases (e.g. chronic gastritis, arrhythmia, thyroid disease etc.) were observed in less than 5.7% of all the patients. Interestingly, none of the COVID-19 patients in Wuhan, regardless the disease severity, reported bronchial asthma, allergic rhinitis or atopic dermatitis [4], while the prevalence of allergic airway diseases in Wuhan is 4.2% (asthma) and 9.7% (allergic rhinitis), respectively [9,10].

This lack of susceptibility to COVID-19 in patients with pre-existing asthma and allergic airway disease appears in contrast with the established link between these chronic respiratory conditions and susceptibility to common respiratory viruses, especially rhinoviruses [11,12].However, rhinovirus uses the ICAM-1 molecule as an entrance into respiratory epithelial cells [13], which is overexpressed in allergic airways as a marker of allergic inflammation [14]. In contrast, COVID-19 uses another host cell receptor abundantly present in the oral mucosa and within the (healthy)airways, i.e., the angiotensin-converting enzyme2 (ACE2)[15,16], whichplays a crucial role in the disease development and associated lung injury [17,18]. ACE2 is a homologue of angiotensin converting enzyme (ACE). ACE activity and certain gene polymorphisms are positively correlated to clinical manifestations of asthma or COPD. As compared with those on maintenance therapy with inhaled corticosteroids (ICS), lower expression of ACE has been found within the airways of asthmatic patients not treated with ICS. Moreover, low ACE expression within the bronchial epithelium wasinversely associated with eosinophilic infiltration within asthmatic airways [19]. Previous data showed that the homeostasis between ACE and ACE2 is crucial for lung damage and ACE2 probably could represent a protective factor under certain conditions[20].Hence, ACE2 probably has a double effect on SARS-induced lung injury: initially, it serves as a receptor for invading coronavirus, while its subsequent downregulation promotes lung injury [18].Expression of ACE2 is increased inpatients with type 1 and type 2 diabetes mellitus and patients with hypertension treated with ACE inhibitors (ACEi) - i.e. ACE2 stimulating drugs. This could explain the increased risk of COVID-19 in patients with diabetes or hypertension reported in some publications [4,21]. On the other hand, recently published reports suggested also possible protective role of the inhibitors of renin-angiotensin system [22]. In a recent trial, these agents increased $CD3^+$ and $CD8^+$ T cell counts and decreased the peak viral load compared to other antihypertensive drugs in patients with hypertension and COVID-19 [23].

Currently, the theoretically increased risk for COVID-19 in patients treated with ACEi was not proven by clinical studies and is based only on a hypothesis. Therefore, professional societies strongly recommend to continue the treatment of ACEi.

Another remarkablefindingis the high proportion of COVID-19 patients (in general but especially in the severe cases) with leukopenia and lymphopenia (including eosinopenia)[2,4,6,26,33,34]. Guan et al. found leukopenia (< $1.5x10^9$/L)in 83.2% patients on admission [5]. Patients with severe COVID-19 disease had more prominent laboratory abnormalities including lymphopenia and leukopenia compared to those with non-severe disease [5]. The proportion of leukopenic patients varied across studies from 3% to 83.2%, but usually was found in more than 50% of patients [34]. The number of T-cells was significantly decreased, especially T helper (Th) cells in severe patients[26]. Another group also reported decreased $CD8^+$ and $CD4^+$ T cells in COVID-19 patients with pneumonia [27], whilelow numbers of $CD4^+$ T lymphocytes were associated with prolonged detection of viral RNA in patients' stool [28]. $CD4^+$ Th cells are more important in the control of COVID-19 than $CD8^+$ T cytotoxic lymphocytes [29]. The major changes in immune system parameters observed during COVID-19 infection sofar are summarized in **Table 1**.

Considering the anti-viral effects of eosinophils [30-32], the reported eosinopenia in COVID-19 patients is of special interest. So far, at least fivestudies reported on blood eosinopenia in a majority of the COVID-19 patients [4,6,26,33,34]: i.e., 52.9% (73/138) [4], 70% (7/10) [6],90% (9/10) [33], and 81.2% (69/85) [34], respectively (**Table 2**), while no data on this topic have been presented by other available literature. In the study of Zhang et al. (2020), blood eosinopenia was observed in more than half of the patients, both in severe and less severe cases [4]. Normalization of the eosinophil number signalled the improvement of the clinical status in another case series [33]. Conversely, in a series of 85 fatal COVID-19 cases, a substantial number of the patients showed profound and persistent eosinopenia [34]. As suggested by the authors, decreased blood eosinophil counts may serve as a potential indicator of COVID-19 infection and may have an important diagnostic value, especially in patients with respiratory symptoms and radiological changes such as ground-glass opacities in the lung bilaterally [4]. In the context of recent evidence of antiviral effects of eosinophils, the observed eosinopenia could be either the sign of host exhaustion due to clearance of invaded COVID-19 or the primary risk factor for severe and invasive infection with this virus.On the other hand, among the cytokine profile pattern associated with COVID-19 (especially severe cases), classic eosinophil-driving cytokines are

missing (e.g. IL-5) [2]. Whether the eosinopenia is the consequence of Th1/Th2 imbalance or induces it remains unclear. However, increased production of TNF-α shifts the spectrum of cytokines produced by eosinophils towards Th1 response (e.g. anti-viral IFN-γ) with the lack of classical Th2 cytokines [35]. It could be speculated that this could be one of the reasons of low incidence of asthmatics among COVID-19 infected patients. Moreover, the reported Th17 inflammatory signature in severe COVID-19 patients [36] could be the result of the lack of the suppressing effect of themissing or dysfunctional eosinophils [37].

Based on the current evidence and clinical observations, it could be suggested that allergic airway diseaseassociated with eosinophilic infiltration and down-regulation of ACE2does not represent a risk factor for COVID19 infection. Further investigations are highly needed to confirm mechanisms underlying the low prevalence of allergies and chronic inflammatory/respiratory diseases in COVID-19 patients and to clarify the clinical meaning and therapeutic consequences of eosinopenia in these patients.

Milos Jesenak[1,2], Peter Banovcin[1], Zuzana Diamant[3,4]

[1] Department of Paediatrics, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia

[2] Department of Clinical Immunology and Allergology, University Teaching Hospital in Martin, Slovakia

[3] Department of Respiratory Medicine and Allergology, Institute for Clinical Science, Skane University Hospital, Lund University, Lund, Sweden

[4]Department of Respiratory Medicine, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic

Corresponding author: Milos Jesenak

jesenak@gmail.com

Conflict of interests:

MJ received honoraria, consultancy and speaker fees from ALK, Stallergenes-Greer, MSD, Sanofi-Genzyme, Sanofi-Pasteur, Angelini, GSK, Novartis, Nutricia, Nestle, Mundipharma, Berlin-Chemie, CSL Behring, Hero.

PB declared no conflict of interests.

ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies and received honoraria, consultancy and speaker fees from Acucort, AstraZeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, Sanofi-Genzyme.

Authorship:

MJ was involved analysis and interpretation of the data, in drafting and revising the manuscript.
PB was involved in interpretation of the data and in revising of the manuscript.
ZD was involved in analysis and interpretation of the data discussed in the manuscript and in revising the manuscript.
All the authors approved the final revised version of the manuscript.

Table 1: Summary of reported changes in immune/inflammatory parameters during COVID-19 infection.

Parameter	**References**
Lymphopenia (in 3 – 75% of COVID-19 patients)	[2,4,5,6,8,9,26,33,34]
Eosinopenia (in 52.9 – 90% of COVID-19 patients)	[4,6,26,33,34]
↓ $CD3^+$ T cells, $CD4^+$ T helpers, $CD8^+$ T cytotoxic cells	[8,26,27,28]
↓ memory T helper and ↑ naïve T helper cells	[26]
↓ T regulatory cells	[26]
↑ IL-10 and IL-6	[26,27]
↑ IL1β, IL1RA, IL7, IL8, IL9, IL10, FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, VEGF	[2]

Table 2: Summary results of eosinopenia in the reported trials (based on the availability of the data in the publications).

Ref.	**Normal reference range** [$x10^9$/L]	**Eosinophils** [$x10^9$/L]			**p***
		All	**Non-severe patients**	**Severe patients**	
[4]	0.02 – 0.52$x10^9$/L	0.01 (0.0 – 0.05)	0.02 (0.008 – 0.05)	0.01 (0.0 – 0.06)	0.451
	Proportion of patients	73/138 (52.9%)	39/82 (47.6)	34/56 (60.7%)	0.165
[6]	0.02 – 0.52$x10^9$/L	0.01 (0.01 – 0.01)	-	-	-
	Proportion of patients	7/10 (70%)	-	-	-

[26]	0.02 – 0.52x10^9/L 0.4 – 8.0%	0.0 (0.0 - 0.0) 0.0 (0.0 – 0.4)	0.0 (0.0 – 0.0) 0.2 (0.0 – 0.7)	0.0 (0.0 – 0.0) 0.0 (0.0 – 0.2)	<0.001 <0.001
[33]	0.02 – 0.52x10^9/L	Eosinopenia in 9/10 (90%)	-	-	-
[34]	0.02 – 0.52x10^9/L	0.013±0.025**	-	0.013±0.025	-
	Proportion of patients	69/85 (81.2%)	-	69/85 (81.2%)	

* Comparison between severe and non-severe cases

** Series of 85 fatal cases of COVID-19

References:

1. Dong X, Cao YY, Lu XX, et al. Eleven faces of coronavirus disease 2019. Allergy 2020; doi: 10.1111/ALL.14289.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
3. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infection 2020; doi.org/10.1016/i.jinf.2020.02.016.
4. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-COV2 in Wuhan, China. Allergy 2020; doi: 10.1111/all.14238.
5. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; doi: 10.1056/NEJMoa2002032.
6. Li YX, Wu W, Yang T, et al. Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19. Zhonghua Nei Ke Za Zhi 2020;59:E003. Di.:3760.10/cma.j.cn112138-20200221-00114.

7. Lupia T, Scabini S, Pinna SM, Di Perri G, De Rosa FG, Corcione S. 2019-novel coronavirus outbreak: a new challenge. J Glob Antimicr Res 2020; doi.org/10.1016/j.gar.2020.02.021.
8. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; doi: 10.1001/jamainternmed.2020.0994.
9. Huang K, Yang T, Xu J, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet 2019;394:407-418.