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Interaction between SARS-CoV-2 and human organism

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Abstract

Background: COVID-19 is a part of the betacoronaviridae group, sabercoviridae subgroup. At the moment we are confronting a pandemy, which has a completely new pathologic pattern for the whole world. Considering the highly contagious characteristics of the virus, which is the cause of death for many people, and also the fact that many people continue to be infected with this virus there is a stringing necesity of combating this pandemy. Because of that we need the knowledge that regards the physiopathologic mechanisms, particularities of the host-invader interactions, relevance of asymptomatic forms, explanations of the evolving divergencies, posibility of recurrent infections, clinical signs, comorbidities that harshen this pathology, pharmacologic agents that are effective to fight the infection and immune mechanisms of defense in the organism. A great importance is given for the identification of the intial criteria needed for a prognostic, to prevent the critical forms of pathology and to set the parameters for the severity indicators.
Conclusions: The research in the field of SARS-CoV-2 requires the gathering of the databases that are related to the investigated persons, to establish the clinico-evolutive differences for the COVID-19 patients according to many factors that could influence the course of the disease. An important difference is the identification of early signs and prevention of the critical disease forms, by extending the laboratory investigations, establishing the parameters for severity indicators through determining the degree of the immune response.
Key words: COVID-19, SARS-CoV-2, Coronavirus.

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Introduction

Starting from 2020, the international medical community directed its attention towards the new coronavirus, COVID-19 and the pathology that it determines – SARS-CoV-2. This virus appeared for the first time in the city of Wuhan, Hubei province, China and has spread very fast at a global level. The hastened spread of this virus puts the world into the evidence of the high transmissibility of this family of viruses with a significant mortality and morbidity. As this virus appeared recently, it needs a continuous research. We are in a continuous pandemy with COVID-19, scientists are fighting to understand the similarities and differences between COVID-19 and SARS-CoV-1 at genomic and transcriptomic level [1]. The main targets of the virus are the lungs, but it has a serious effect on heart especially in case of a cronically affected one that needs a supplementary effort in order to deliver the oxygenated blood to the tissues. Patients with persistent cardiac affections have a weaker immune system. The immune response is decreased when advancing in age and in people with chronic comorbidities. One of the objectives of this study was to present the most recent data in order to determine the immune response in patients with COVID-19.

To realize this objective we used the Google Search results and the PubMed database. For advanced search of the bibliographic sources we applied the following filters: articles with integral texts, articles in the English language published before 28.04.2020. After a preliminary analysis of the titles we selected the original, editorial articles of narrative synthesis, systematic and meta-analysis that contained relevant information and contemporary concepts about COVID-19. The information of the publications included in the bibliography was collected, classified, evaluated and synthesized putting into evidence the main aspects of the contemporary visions about the infection and immunity in COVID-19.

Results and discussion

The SARS-CoV-2 virus is entering the organism via the ACE2 [2-10] that is intensely expressed in the cells of the nasal mucosa, bronchi, lungs (type I and type II alveolocytes), heart, esophagus, kidneys, stomach, billiar sac, ileon, and neurons [5, 7, 8, 10]. After the invasions, the celullar proteases (TMPRSS2 and Furing) will lead to the final internalisation of the virion [11].

The anterior situses are the most affected in case of SARS-CoV-2, the epithelial cells being distructed after the invasion [12]. The supposed enter gates are – the respiratory epithelia at pulmonary level [7], through the olfactory fillia that are penetrating the lamina cribrosa [5, 13]

or through the nervous fibers of the pulmonary mechano- and chemo-receptors via the nucleus *tracti solitarii* and the neuroinvasion can also take place through the limphatics [13]. The specificity for this receptor was conferred by the spike glycoprotein that has the S1 and S2 subunits that are attached to the viral envelope (capsid) [1, 4, 5, 14, 15]. There are numerous polimorphisms for this protein in the same viral species, thing also characteristic for COVID-19 [1], the spike protein is expressed 10-20 times more intensely by COVID-19 comparatively with SARS-COVID-1, the fact argumented by the enhanced viral permeability [5, 16]. Another way of cell invasion is through the CD147 receptor (Basigin/EMMPRIN) via the spike-CD147 protein [17], another membranary receptor that could stimulate the matrix metalloproteases (MMP) – MMP1, MMP2, MMP3, MMP9 [18, 19], because of this COVID-19 could affect the T lymphocytes [20]. Once entered in the cell, the virus starts the translation of the own ARN for the pp1a and pp1ab proteins codified by the ORF1a and ORF1b genes – that play a key role in the viral replication, that are cleaved by the nsp 1-16 proteins [14, 21], respectively the inhibition of this chain could signifcantly decrease the infecting potential in the host. The antigens characteristic for COVID-19 can be recognized by the following receptors in human body – Toll-like receptor (TLR), Nod-like receptor (NLR), pattern recognition receptors (PRR), RIG-1 like receptor (RLR) and the cytolosic receptor for melanoma differentiation-associated gene 5 (MDA5) [4, 14] that are on the surface of the antigen presenting cells and also interact with the CD26, cyclophilin enzime [15]. This leads to the release of the pathogen-associated molecullar patterns (PAMP) [14], that could interact with the cells of the human organism in order to unleash the formation of inflammasomes that lead to the apoptosys through the NF-κβ pathway intracellulary and will determine the local inflammation of tissues that in the most severe cases will determine the systemic inflammatory response syndrome (SIRS) [22], along with the acute respiratory distress syndrome (ARDS), trombosys and pulmonary embolism [12]. In the infection with SARS-COVID-1 we observe a hiperglicemy, reffering to the infection with SARS-CoV-2 we haven't observed such modification at the moment [11]. During the febrile syndrome manifestion eczematous eruptions may appear [23, 24] or vesicles surrounded by erythematous halos that could form crusts – that are located preponderentely in the thoracic region [25], [42]. Lesions characteristic for frostbites were identified for the most patients with SARS-CoV-2 without confirming their association with the respective infection [26]. More recentely we have a report of the acral cutaneous lesions [27].

An incidence of 1% of conjunctivitis was reported in a meta-analysis [28]. Along with the spike protein, COVID-19 presents the hemaglutinin-esterase, membranary protein M, nucleocapsidic protein, the small capsidal protein, the internal protein and specific group protein – potential targets for vaccines [29].

In SARS-CoV-2 the activation of the CD8+ lymphocytes and CD4+ lymphocytes is being observed along with the C3a and C5a components of the complement that play a major role here, the worst scenario being the systemic inflammatory response syndrome (SIRS) with multiple organ dysfunction syndrome (MODS) [1, 2, 4]. In SARS-CoV-2 was observed the cytokine storm [10, 30]. In the plasma of the patients with SARS-CoV-2 we identified the following cytokines – IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17 and the colony stimulating factor of granulocytes (G-CSF), the macrophage colony stimulating factor (M-CSF), IP-10, MCP-1, MIP-1α, the hepatocyte growth factor (HGF), IFN-γ and TNF-α [13, 14], particularily we see the presence of the interferon 1 (IFN1) that plays a major role in the inhibition of the Th1 differentiation and the amplification of the Th2 cells, chemokines like IP-10 and MCP-1 that are intensely expressed in the COVID-19 [13, 30] will determine the chemotaxis of the numerous cells of the immune system, especially the neutrophils that will cause diffuse alveolary lesions and ARDS [1-3, 10, 13, 30]. The severe cases have a basal lymphopenia, leucocytosis an increased neutrophil/lymphocyte level and less monocites, eosynophils and basophils. The number of Th lymphocytes is decreased, the number of Ts lymphocytes is decreased, the number of naive Th circulant levels is increased, the number of Th lymphocytes is decreased [9, 31] this is explainted by the fact that COVID-19 could enter these cells via the CD147 [20]. Th lymphocytes express the Notch1 gene [32], having a high fraction of fatigued T lymphocytes [12]. The serin proteases and cathepsins are released during the immune response and could cleave the spike proteins – reducing the viral permeability [14]. The levels of Angiotensin II is positively correlated with the viral dose and the severity of lesions because it denotes the high levels of ACE receptors expression and hastens the ARDS installation [3]. The ORF1ab, ORF10 and ORF3a proteins could coordinate the hem attack in the β1 chain of the hemoglobin and "steal" the Fe ions from the hem, also the capsidal glycoproteins could bind to the porphirinic chain [33], a meta-analysis has shown that patients with SARS-CoV-2 have a decreased total hemoglobin [34]. An increased level of C reactive protein (PCR) is observed because of the systemic inflammation, an increased level of feritin because of the hem attack and an incresed level of procalcitonin due to the response to the infection in the organism [35]. At the cardiac level an acute cardiac lesions could appear [36], that could evolve in a cardiogenic shock having an elevated concentration of troponin. The mechanisms of proposed lesions are – myocardial hypoxy, the distruction of the microcirculation vessels, endothelial descuamation and cytokine mediated lesions – there are no proofs at the moment that the myocardium could be infiltrated with lymphocytes, the global effects are represented by the cardiac failure, arrythmia and cardiac decompensation [29]. Taking into consideration that the dopamin decarboxylase gene is positively correlated with the ACE2 gene, we could suppose that alterations in the synthesis of the dopamine are correlated with the physiopathologic mechanisms of the COVID-19 [37]. At the initial stages it could cause anosmia, ataxia and convulsions – in the most severe cases it could lead to respiratory stop [38].

The infection starts with the activation of the dendritic cells that reside in the pulmonary tissue, that will present further the antigens to the naive T cells that will secrete different chemokines and cytokines [29], the CD8+ cells have the tendency to secrete high quantities of IL-6 and the CD4+ have the tendency to secrete high quantities of IFN-γ and GM-CSF [12, 29] but they could secrete the chemokine ligand 9,10 and 11 (CXCL) and cytolytic molecules just as granzyme B [29]. A series of comorbidites could make the infection with SARS-CoV-2 worse, like arterial hypertensions, determined by the amplification of the renin-angiotensin-aldosteron system (RAAS) by inducing endothelial lesions that will lead to cardiac, pulmonary and renal complications [3, 14, 39]. It can induce the distruction of the hemato-encephalic barrier; the cerebrovascular pathologies will worsen the SARS-CoV-2 flow [5, 39]. The pulmonary pathologies (Chronic obstructive pulmonary diseases – COPD), diabetes mellitus and advanced age were recognized as risk factors [7, 11, 14], in diabetes mellitus an increased expression of ACE2, furin was observed along with the dysfunction of the CD4+ cells and increased concentration of IL-6 [11], furin being codified by the Notch1 gene [32]. The patients with respiratory insuficiency need on-stage intubation [40]. The infection has weaker manifestions in children because they are temporary adapted in order to combat the viral infections, also the ACE2 receptors are less pronounced in their organism [9, 12], the male gender has a more severe symptomatic because of increased ACE2 expression [12]. Patients with pulmonary cancer are more susceptible to COVID-19 infection [41]. We have to mention that along with the generic symptoms of SARS-CoV, although we mentioned before about dermatological findings, we can observe chicken-pox like vesicles [42] and an increased level of lactate-dehidrogenase (LDH) and creatinfosfokinase (CPK) [3]. We reported a case in which an asymptomatic woman that presented an infection with COVID-19 in the tardive partum period hasn't transmited the virus vertically [43].

The long-term consequences after SARS-CoV-2 infection at the moment are not known in details, but it was reported that in 40% of the patients with SARS-COVID-1 were observed cardiovacular anomalies and dysregulations of the lipidic metabolism [44].

A series of pharmacological agents are potentially efficient for combating SARS-CoV-2 infection, we will expose a part of them: Baricitinib [30, 45], Ruxolitinib and Fedratinib are inhibitors of JAK-STAT signaling and respectively it wouldn't diminish the systemic inflammatory effects in SARS-CoV-2 [45]. Chloroquine is supposed to be a strong antiviral agent, useful in the treatment of pneumonia caused by COVID-19, being very economic from the financial point of view [9, 21, 30, 46, 47], it is very effective to inhbit the distruction of hem by the ORF1ab, ORF3a and ORFa proteins along with the capsidal glycoproteins [33]. Hidroxychloroquine (HCQ) could glycosilate the ACE2 receptors, it could induce the cleavage of the spike proteins and block the cytokine storm, but the Ivermectin – an antiparasitary agent could interfere with the nuclear transport of the viral proteins dependent on the α/β importin, a combination of HCQ/Ivermectin is recognized to be used in order to combat SARS-CoV-2 but we haven't conducted a study about its effect [48]. The efficiency of Ivermectin in SARS-CoV-2 was tested only *in vitro* at the moment (14.04.2020) [49]. Erythropoietin has shown its efficiency in order to combat the enemy caused by SARS-CoV-2 in case study [50], also in a theoretic review there are proposed the pharmacological agents used in case of pulmonary edema caused by high altitudes (EPAM) – acetazolamide, nifedipine and inhibitors of phosphodiesterase without being clinically tested at the moment [51]. The inhibitors of the viral proteases (nsp inhibitors) like lopinavir and ritonavir are potential antiviral agents that could combat this infection [21], a combination of lopinavir-ritonavir was used to combat SARS-COVID-1 and MERS-COVID [52]. Favipiravir could inhibit the binding of the spike and ORF7a proteins to the porphirin ring [33]. Corticosteroids are potential antiinflammatory agents [30], but the corticosteroids determine an increase in the spread of the virus into the organism [13]. The inhibitors of the interleukin-6 could be useful in order to combat SARS-CoV-2 [9], the results of a clinical study show that the administration of tocilizumab (an inhibitor of IL-6) could be useful in order to combat COVID-19 if it is administered many times [53]. At the moment the inhibition of Notch1 gene is discussed in order to prevent the cytokine storm [32]. A study made *in vitro* proves that the multiplication of COVID-19 is inhibited via the blockage of CD147 with agents like Meplazumab [17, 54]. Azithromycin can inhibit the action of some matrix metallproteinases. AS the STEM cells present a CD147 receptor, they could also serve as a target for SARS-CoV-2 [18], being proved to be a good adjuvant agent along with hydrocholoroquine in a non-randomised clinical study [55].

The identification of the viral dose from the salivary prelevate taken from the posterior oropharyngeal mucosa could be an efficient method to determine COVID-19 at an incipient stage of manifesting SARS-CoV-2, but it is necessary to combine this inspection with an antibody analysis because they present an inverse correlation with the viral dose [52]. In the blood plasma consequently there are antibodies with a median seroconversion on the 11th day, IgM with a median seroconversion on the 12th day and IgG with a median seroconversion on the 14th day ($p<0.05$), the tests for the antibodies could be useful in order to assess clinical suspections in the symptomatic patients that don't have a viral ARN detectable in plasma [56]. The administration of convalescent plasma for the patients with SARS-CoV-2 was proven to be efficient to attenuate the infection manifestations, according to a theoretic review in a series of cases, at the moment there are no avaible randomised clinical trials (RCT) [57]. The antibodies in SARS-CoV-2 infection could be detected only in the medium and late stage [58]. The patients that could recover after an infection of SARS-CoV-2 could have high viral doses in the fecal masses [59].

At the moment the histopathological aspects of SARS-CoV-2 are not yet known in details, according to a theoretic review, the patients with pulmonary cancer presented histopatological patterns- macroscopic (pleurisy, pericarditis, pulmonary consolidations and edema) and microscopic (alveolary proteic exsudates, focal reactive hiperplasia of the pneumocytes with grouped celullar infiltrations and gigantic polynucleated cells without hyalin membranes). The patients that presented the ground glass image on the pulmonary radiography, had diffuse alveolar lesions with exsudates (characteristic for the distant lesions of immune systems in SIRS). No viral inclusions were detected in the histopathological findings [60]. Diffuse alveolar lesions were observed in another study, along with infiltrates of CD8+ lymphocytes and CD4+ lymphocytes around the high caliber bronchioli, in the majorty of cases being present hemoragic foci and intracelular trombi, type II pneumocytes with cytopatic effect (desquamed), the alveolar capillaries were hypertrophiated with perivascular edema, in this case there was no hyaline membrane but were identified CD61+ megacariocytes. In the heart we identified disseminated celullar necrosis, without focal accumulations [61]. The ground glass image in the pulmonary radiopgraphy identified diffuse alveolary lesions in the organizatoric phase, fibrinous alveolar proteic exsudate, hyperplasy of the reactive pneumocytes type II along with interstitial fibrosis and chronic inflammatory infiltrations [62]. At the renal level there were acute lesions of the proximal tubule manifested with vacuolar degeneration and epithelium desquamation. For the patients with pathologic pulmonary manifestation we identified the acute pyelonephritis, more rarely – erytrocitary aggregation in the tubes with consequent obstruction, ocasionally we observed the hemosiderin inclusions. The distal tubules didn't present serious pathological modifications [63].

Conclusions

SARS-CoV-2 became a global threat for health, with the number of patients increasing gradually. An increased incidence of diverse comorbidities was observed along with those that presented severe infection. The mechanism of cardiac lesions is not clear but it probably implies a combination of direct viral lesions and immunised damage mediated by the inflammatory cytokines/chemokines and cytotoxic response of the immune cells in the further infection stages. The immune response of the host and the contributors to the cytokine storm in the infection with SARS-CoV-2 is complex. The exhaustion and significant deregulation of the T lymphocites could contribute to the immune degradation and hyperactivity. The treatments for COVID-19 are bimodal with a treatment group oriented towards the temporary infection and viral replication, there is also another group that takes into consideration the modulation of the immunity at the systemic inflammatory stage. It is important to make complete immune searches for the patients with diverse comorbidites in order to understand the systemic deregulations better. It is necessary to acquire more data about the immune response according to the severity of disease and to take the needed measures in the managerial acts in the infection control.

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GP conceptualized the project and designed the research; VP revised the manuscript critically. LC interpreted the data; VC performed the laboratory work; LP drafted the manuscript; DC drafted the manuscript and designed the research. All authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
No approval was required for this study.

Conflict of Interests
No competing interests were disclosed.