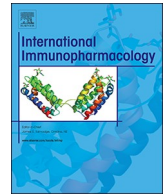




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Short communication

SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment



Gabriella di Mauro^{*,1}, Cristina Scavone¹, Concetta Rafaniello, Francesco Rossi²,
Annalisa Capuano²

Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Regional Centre of Pharmacovigilance, Campania Region, Naples, Italy

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ABSTRACT

The new coronavirus outbreak is an ongoing pandemic that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The new coronavirus SARS-Cov-2 belongs to the subfamily of β -coronaviruses and shares 79.5% of the genetic sequence of SARS-CoV, the causative agent of the epidemic that started in 2002 and ended in 2004.

Considering the clinical impact of the new outbreak, it is highly important to study the potential responses of the human immune system during the SARS-CoV-2 infection as well as the role of virus-specific T cells and by B-lymphocytes. Moreover, specific data on the production of IgG and IgM is crucial to allow the rapid identification of the infection. In this paper we also described the importance of sensitive and specific rapid test for SARS-CoV-2. Indeed, this test represents an important immunological tool aimed at identifying the precise phase of the infection in order to undertake a more appropriate pharmacological treatment. Lastly, we provided an overview of pharmacological treatments aimed to reduce inflammatory processes underlying the infection and the need for the discovery of a new vaccine against SARS-CoV-2.

The SARS-Cov-2 virus belongs to the family of coronaviruses, positive-stranded RNA viruses that are characterized by a spherical shape, which provides them the typical "crown" appearance. These viruses were first identified in the mid-1960s and classified into four distinct subfamilies: α - β - γ - δ -Coronavirus. Alpha and beta-coronaviruses mainly infect mammals, while gamma and delta-coronaviruses are more inclined to infect birds [1]. Some of them can induce a mild infection in the upper and lower respiratory tract, while others can cause serious symptoms that can lead to respiratory failure. To date, seven types of coronavirus able to infect humans have been identified: the most common are HCoV-OC43 and HCoV-HKU1 (β -coronavirus) and HCoV-229E and HCoV-NL63 (α -coronavirus). These viruses can cause common colds but also severe lower respiratory tract infections. Apart from these, three other beta coronaviruses, called SARS-CoV, MERS-CoV and 2019-nCoV (SARS-CoV-2), have been identified. The new coronavirus SARS-Cov-2 belongs to the subfamily of β -coronaviruses and shares 79.5% of the genetic sequence of SARS-CoV, the causative agent of the epidemic that started in 2002 and ended in 2004.

SARS-Cov-2 infection can occur with fever, fatigue and dry cough

and, in severe cases, with pneumonia, acute respiratory syndrome, and kidney failure. In some cases SARS-Cov-2 infection can be fatal. Considering immunopathological aspects, about 80% of patients with SARS-CoV-2 infection experience mild or null symptoms. However, in severe cases patients may experience lymphopenia and interstitial pneumonia with high levels of pro-inflammatory cytokines including IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1 α and TNF α . As a result, the massive release of cytokines generates the so-called "cytokine storm" which, in turn, can induce acute respiratory distress syndrome (ARDS), respiratory failure, organ failure and potentially the patient's death. This mechanism is the basis of the rationale for the administration of tocilizumab, a monoclonal antibody that inhibits ligand binding to the human interleukin-6 receptor (IL-6R), which was recently approved in China to reduce lung complications in patients with SARS-CoV-2 infection [2]. Apart from tocilizumab, which counteracts inflammatory phenomena deriving mainly from activities of IL-6, other drugs, mainly represented by antivirals (the combined treatment lopinavir/ritonavir, remdesivir, favipiravir, umifenovir), are currently under evaluation for the treatment of SARS-Cov-2 [3]. For

* Corresponding author.

E-mail address: gabriella.dimauro@unicampania.it (G. di Mauro).

¹ These authors have equally contributed.

² These authors are both lead authors.

instance, recent data shared by the Italian Ministry of Health revealed that, among those medications, the combined treatment lopinavir/ritonavir is currently used in Italian hospitals for the treatment of patients with SARS-CoV-2, while remdesivir is currently evaluated in two phase 3 clinical trials in Italy. On the other hand, the use of favipiravir is under evaluation by the Italian regulatory agency (AIFA) [4].

Several studies are currently investigating the potential response of the immune system during the SARS-CoV-2 infection. Most of these have already shown that, during the infection, patients develop an uncontrolled immune response, caused by the hyperactivation of macrophages and monocytes. This response results in an increase in neutrophils, IL-6 and reactive protein C (PCR) and in a decrease in the total number of lymphocytes [5]. As for all viral infections, in the adaptive immune response, virus-specific T cells, for cell-mediated immunity, and by B-lymphocytes, for humoral immunity, play a key role. Indeed, the activation of Th1/Th17 by Helper T lymphocytes can contribute to the exacerbation of the inflammatory response, while B lymphocytes provide for the production of specific antibodies for SARS-CoV-2 aimed at neutralizing the virus. It is widely recognized that prior to the production of high affinity immunoglobulins G (IgG) for long-term immunity and immunological memory, M immunoglobulins (IgM) provide the first line of defense during viral infections. Accordingly, the detection of IgM in the serum reveals a recent exposure to the virus, while the detection of IgG suggests that the exposure occurred several days before. However, specific data on the response of human immune system during the SARS-CoV-2 infection are still lacking and most of these are based on the knowledge acquired in the past years during SARS-CoV and MERS-CoV infections [6]. It was reported that after SARS-CoV infection, IgM could be detected in patients' blood after 3–6 days, while IgG could be detected after 8 days [7]. Similarly, for MERS-CoV infection, seroconversion was observed at the second or third week of disease onset [8]. For both types of coronavirus infection, delayed and weak antibody response was associated with severe outcomes. Thevarajan et al. defined a potential mechanism implemented by the immune system in the course of SARS-CoV-2 infection [9]. The study was carried out using blood samples from a 47-year-old patient who returned from Wuhan with symptoms that included lethargy, sore throat, dry cough and fever. Blood samples were taken in 4 different stages of the disease, before and after recovery. The results revealed that IgM and IgG progressively increase from day 7 to day 20. Specifically, the researchers showed that 7–9 days after the onset of symptoms, high concentrations of specialized T helper cells (Th), Natural Killer cells (NK) and B cells were detected in the blood sample. This study revealed that in a patient without concomitant diseases, SARS-CoV-2 infection triggers an immune response very similar to that observed during the MERS-Cov infection and that early adaptive immune responses may be related to better clinical outcomes.

Similarly, Zhou et al. found that a patient developed a virus-specific IgM peak 9 days after the disease onset and that the transition to IgG occurred within the second week [10]. In order to apply a rapid test able to detect the presence of specific IgM and IgG for SARS-CoV-2, it is important to consider that the IgM values tend to disappear within 2 weeks since the beginning of the infection. Therefore, considering that symptoms of the infection can occur within 14 days, in most cases it is difficult to accurately determine when a patient contracted the virus. Consequently, if immunoglobulin values are not high enough at the time of the test, false negatives could be recorded [10]. SARS-CoV-2 infection can also be transmitted among asymptomatic patients, who can have a high viral load without showing any symptoms. This is why it is quite difficult to manage the spread of the virus. In order to solve this problem, the use of rapid tests for the combined detection of IgG and IgM would be desirable. These rapid tests are able to simultaneously detect the presence of IgM and IgG in the serum within 15 min and can predict which stage of patient's infection. The sensitivity and

specificity of these tests were evaluated on 397 blood samples from patients who tested positive for the nasopharyngeal swab for SARS-CoV-2 infection and on 128 patients who tested negative and asymptomatic but potentially at risk of developing the infection based on epidemiological criteria [7]. The results of the study showed that out of 397 blood samples from patients with a SARS-CoV-2 infection, 352 tested positive. On the other hand, 12 of the 128 blood samples with SARS-CoV-2 nasopharyngeal swab negative tested positive as well. Therefore, the test showed a sensitivity of 88.66% and 90.63% in the first and second group of patients, respectively. Furthermore, 64.48% of positive patients (256/397) had IgM and IgG antibodies simultaneously. Therefore, the rapid test for the combined detection of IgG and IgM specific for SARS-CoV-2 proves to be sensitive and specific. However, they are not 100% certain, so the risk is register false positives or false negatives cases. At the moment this test represents an important immunological test aimed at identifying the precise phase of the infection in order to undertake a more appropriate pharmacological treatment. Therefore, it is desirable that these rapid tests become more sensitive and specific, in order to quickly identify patients with SARS-CoV-2 and prevent the rapid transmission of the virus.

Lastly, the development of a vaccine against SARS-CoV-2 is urgently needed. According to Shang W et al., the combination of subunit vaccines with adjuvants may represent a good strategy to speed up the clinical development. Authors also reported that researchers would bring a new SARS-CoV-2-based vaccine in approximately 16–20 weeks [11]. While waiting for a specific vaccine, a similar approach to that used for immunotherapies in the treatment of cancer and serious viral respiratory infections could represent an option for the prevention and treatment of SARS-CoV-2. For instance, a solution could be represented by the passive immunization, which is the administration of serum containing specific antibodies taken from patients from SARS-CoV-2 [12]. Unlike active immunization, this approach does not require the activation of the recipient's immune responses and generates an immediate immune response. However, this would be an emergency solution and not a substitute for any vaccination therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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