

Possible Treatment of Seriously Ill Patients with COVID-19, from the Immunological Point of View

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Citation: Navarro-Zorraquino M (2020) Possible Treatment of Seriously Ill Patients with COVID-19, from the Immunological Point of View. J SARS-CoV-2 COVID. 1:001.

Volume 1	Issue 1
Pages	1-2
Received	📅 July 23 , 2019
Accepted	📅 August 07, 2020
Published	📅 August 10, 2020

COVID-19 pandemic is leading to a large increase in mortality in the elderly population, with regard to mortality rate observed in patients below 70 years infected with ". Mortality rate is dramatically alarming in the case of patients older than 80 years, about 30% compared to the total population of patients infected by COVID-19.

From an immunological point of view, I do think that it must be pointed out this: elderly patients can present significant alterations in their immune response when their immune system is challenged by infections, accidental or provoked trauma (in the case of surgical interventions, especially those that cause greater tissue damage). Since 1975, our research group has conducted numerous studies on elderly patients undergoing accidental or surgical trauma and infection; our results have led us to the following conclusions: defects in the immune response in the elderly may be related to thymus involution, but above all, to the alteration of the balance between "pro-inflammatory response" and "anti-inflammatory response" mediated by regulatory lymphocytes.

When macrophages or any others "antigen presenting cells" are stimulated, the quintessential "pro-inflammatory" cytokines are released: IL-1, IL-6, IL-8, TNFs, IFN γ and PAF (activation factor platelet), etc. These cytokines have a relevant role in the inflammatory process and they, in turn, can give rise to the so-called "cytokine storm", the consequence of which is the "systemic inflammatory response syndrome" (SIRS) and finally the "multi-organ failure" (MOF), conducting to death.

As Niels Jerne said: "any stimulus capable of producing an immune response, causes a reaction comparable to the transmission of the waves that can be observed in a pond when a stone is thrown, so that in the immune system, the variation in the receptor site of the stimulus is transmitted to all places". But in the "SIRS" this allegory reaches a dramatic expression and encompasses not only the network of signals, which intersect and intersect within the immune system, but between the different systems (coagulation, fibrinolytic, cyanines, ac. arachidonic, leukotriene thromboxane), the immune system itself (complement system, circulating immune complexes ICC, ADCC, NK cells, immune adaptive response: CTLs and cytokines). For this reason, the lack of control of the servo-mechanisms that maintain homeostasis in any of the mentioned systems can cause an unstoppable situation of mediator release which irretrievably leads to tissue damage.

The lung is the organ most sensitive to aggression resulting from phenomena triggered during the "SIRS" of any kind, due to the in-

volvement of the immune system on other systems and on the various mediators in the "acute respiratory distress syndrome"(ARDS) becoming "severe acute respiratory syndrome" (SARS). In 1992, Welhourn and Young carried out a review study in which they reported on acute lung injury caused by neutrophils, macrophages and mediators of inflammation during septic shock. We know that most viruses have a particular tropism, attacking the organ of their choice, the "coronary-virus" invade the respiratory system. At this time, we know that "the new COV-19" (SARS-CoV-2) invades the lung selectively. However, the kidney and liver are also involved in MOF and death.

Let us also remember here that when the macrophage or any other "antigen presenting cell" is stimulated, the quintessential "pro-inflammatory" cytokines are released: IL-1, IL-6, IL-8, TNFs, IFN γ and PAF (platelet activation factor). These cytokines have a relevant role in the inflammatory process and they, in turn, can give rise to the so-called "cytokine storm", the consequence of which is "systemic inflammatory response syndrome" SIRS and MOF

Despite the undoubted role of IL-1, IL-8 and TNFs in the "SIRS" pathophysiology and "MOF", in terms of cytokine release and effects, all the attention of the last 6 years has been focused on IL-6. The interest in this cytokine lies in the close relationship found between its elevation in serum and different situations that can lead SIRS.

Actually, IL-6 is a family of phospho-glycoproteins with different molecular weights, the biological meaning of which has not yet been completely clarified, so its exact role in the pathophysiology of "SIRS" is still unclear, however its significant production and release during the "cytokine storm" is beyond question.

In patients with COVID-19, the relationship between the degree of immune response against "SARS-CoV-2" and IL-6 level found in their serum, makes the quantification of IL-6 especially interesting during clinical COVID-19 infection; in fact, it is already being determined in some recently starting studies . We think, that IgA, IgE and IL-6 measures in peripheral blood together with clinical course of this disease could be recommended to know the severity of this disease in each period.

From the point of view of the immune response, we think that we should avoid, with all the available means to date, that elderly patients do not trigger "cytokine storm" and "SARS". It would be desirable that, at the beginning of the infection (1-4 first days), these

patients were treated with affected anti-inflammatory drugs, without corticosteroids (example: "metamizole"), and with substances that block the intracellular penetration of "SARS-CoV-2" (example: hydroxy-chloroquine[#]). And 5-7 days post-infection: when the viral load increases (virus replication, rapid generation time and large number of particles produced), treatment with serum of infected and healed patients, containing antibodies against "SARS-CoV-2" could be useful [1-5].

However, the best treatment could be the use of "bio-drugs" preventing "cytokine storm" by restoring the balance: "inflammatory response"/ "anti-inflammatory response". In this sense, the "regulatory T cells" of the immune response play a very important role: CD4⁺25⁺Foxp3⁺ cells and CD8⁺25⁺Foxp3⁺ cells produce the main regulatory cytokine, the "transforming growth factor" (TGF β_1). We think that European research projects on this topic should be developed. Now, since these "bio-drugs" are not currently in the market, antiviral drugs and monoclonal antibodies are being used.

Foot notes

[#]It is currently known that treatment with this drug is not useful, since it is not as effective as expected and can cause tachycardia, which is serious in some cases.

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