Autoimmunity Reviews xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning

1. Pathogenesis

The 2020 coronavirus epidemic is characterized by high infectious rates and relatively high mortality, especially among the elderly over the age of 80. In this issue we published two reports related to the COVID-19 infection [1,2]. In most of those severe cases of coronavirus infection, the clinical expression is characterized not only by a fever, cough and other constitutional symptoms, but also by a clinical constellation including a cytokine storm, respiratory failure and eventually death [3]. Among the aberrant laboratory findings which characterize these clinical expressions, one can find leukopenia, increased liver function tests and ferritin levels reaching the hundreds and sometimes thousands of units. This panoply of findings reminds us of four clinical conditions that we have described in the past under the new syndrome — hyperferritinemic syndrome [4–6]. These four conditions include macrophage activating syndrome (MAS) [4], catastrophic antiphospholipid syndrome (cAPS) [7], septic shock and an adverse reaction to the biological compound anti-CD-28 [8]. This reaction to the drug was observed in a short therapeutic trial published in the *New England Journal of Medicine* in which 6 individuals were hospitalized in the intensive care unit with a cytokine storm following the therapy [8]. All the above conditions are characterized by high ferritin levels, a cytokine storm (especially of inflammatory cytokines such as Il-1, Il-6, Il-17, *etc.*) and a high mortality rate that is over 50%. The 6 hospitalized individuals from the aforementioned anti-CD-28 trial did not die as they were immediately rushed to the intensive care unit [8,9]. In the other 3 conditions, we were able to reduce the morality rate significantly below 50% using combined therapies with corticosteroids, antibiotics, IVIG (intra-venous gamma-globulins) and anticytokinic therapy (anti-IL-1 and/or anti-IL-6) [10–12]. The resemblance between these clinical conditions and those of COVID-19, suggests that the very severe cases of the coronavirus are associated with a clinical picture similar to that of the macrophage activating syndrome (MAS), which is unsurprisingly associated with high levels of ferritin. Therefore, the enigma regarding the high mortally rate associated with COVID-19 is most probably explained by a cytokine storm. Understanding this pathogenetic pathway may lead to better therapy and better survival rates. We will consider this further in our discussion of therapy.

2. Diagnosis (Ferritin, sCD163)

It goes without saying that the diagnosis of a COVID-19 infection is based on the presence of the virus in oro-pharyngeal swabs taken at the right time, as well as on the presence of IgM (and eventually IgG) antibodies against the virus. In severe cases, the clinical picture diagnosis may be supported by the clinical manifestations of severe respiratory failure syndrome, as well as by blood tests indicating leukopenia, increased liver function tests and high levels of ferritin [13]. Additionally, we would also like to suggest to test for soluble CD-163 (sCD-163), which represents the activation of macrophages [14,15], the level of which was found to increase in MAS and to parallel the ferritin level [15].

In the past, we have shown this parameter to be involved in parallel to the ferritin being increased during the acute stage of the inflammation (14, 15). A commercial kit for analysing the sCD-163 is available in the market. The question of the pathogenesis relates to whether the ferritin is just an epiphenoemon that can be used for diagnostic purposes, or is the ferritin involved in the vicious cycle perpetuating and exasperating the inflammation. Recently together with P. Ruscitti et al. [16], we have found the role of the H-chain of the ferritin in activating macrophages to increase the secretion of inflammatory cytokines. Thus the circle is completed on our understanding of the pathogenesis of the hyperferritinemic syndrome including the infection with Covid-19.

3. Therapy (IVIG, anti-IL-1, anti-IL-6)

Due to the very rapid distribution of scientific knowledge today, several optional therapies have been already suggested in a small study scales to be beneficial such as the application of chloroquine (plaquenil), remdesivir and others [3]. However, understanding the pathogenesis of the virus causing the cytokine storm one would recommend the addition of anticytokinic biological agents. Such as anti-Il-1 (anakinra) or anti-IL-6 (tocilizumab (TCZ)). These drugs are available especially in rheumatological autoimmune inflammatory conditions and have very good therapeutic results. But I would like to refer to an additional suggested therapy, namely: IVIG. IVIG which is composed of immunoglobulin extracted from 20,000 healthy normal subjects was reported in the past to be effective in several cases of MAS as well as in septic shock. Previously we have reported that IVIG *per se* contains also panoply of anti-viral antibodies [17]. This knowledge has been used in another epidemic in the past of the West Nile Fever (WNF) in New York, a geographical area that by and large is not exposed to this virus. An IVIG that was generated in Israel - an endemic area for the West Nile Fever virus and extracted from healthy Israeli convalescence blood donors was found to be effective in reducing the morbidity of the West Nile Fever in New York [18–20]. IVIG *per se* can be helpful in an infectious situation by the transfer of a normal innate immune system of healthy subject to the infected individual [21,22]. Having almost no side effects [23], it would be recommended to deliver the IVIG in a dose of 2 g per Kg bodyweight in 4 days (according to the bodyweight of the

https://doi.org/10.1016/j.autrev.2020.102538
Received 31 March 2020; Accepted 31 March 2020

person). Needless to say, that an IVIG produced from a large number of SERA derived from convalescence subjects from the viral infection will be much more effective and could be delivered in smaller doses. Preliminary studies have already been performed in several sites in the world [13]. We would urge to produce what we have called in the past specific IVIG (sIVIG) in which this specific convalescence IgG would be extracted and could be used really in minimal amounts [24–27]. There is a possibility to affinity purify this IVIG either on a column constructed from peptides of the spikes of the virus or from peptides known to be the constituents of the virus as was deliniated by our recent paper [28].

4. Vaccine (Avoid side effects)

We all are expecting the vaccine production trials to materialise quickly. We believe that once the vaccine found to be effective (most probably on a theoretical basis) it will be distributed to millions or billions of people. We believe that this vaccine will be approved through an expedited process thus not necessarily enabling surveillance due to the shortness of time thus eventual side effects of the vaccine could not be evaluated. The amino acid sequences of the virus like in other viruses, might have a cross-reaction with the human body sequences [28–31]. Therefore, one of the side effects of giving a MASS vaccine could be an mergence of autoimmune diseases especially in individuals who are genetically prone for autoimmunity [28–31]. Actually the corronavirus was reported to induce retinal autoimmune disease in an experimental model [32]. We have recently delineated the amino acid penta-peptides of the virus and selected those who are immunogenic yet have no similarities to the human constiuantes and we believe that any vaccine which can be produced by such a method will reduce significantly the eventual side effect of induction of autoimmune diseases [28]. Those immunogenic peptides can also be used to generate an affinity column to extract the specific antibodies to the virus existing in the SERA of convalescence subjects from covid-19. (See section Therapy).

5. Conclusion

Better understanding of the pathogenesis of the infection with the covid-19 which in selected cases may lead to a similar clinical picture of macrophage activating syndrome (MAS) with its associated cytokine storm may bring to an improved diagnostic measurements. Such precisional medicine may help in early diagnosis of deterioration into the severe clinical conditions. Moreover, understanding this pathogenesis may lead to a better therapeutic measurements which may entail also anti cytokinic therapy as well as adding to the therapeutical regiment IVIG. If possible harnessing specific IVIG which is enriched with anti COVID-19 antibodies extracted from the SERA of patients who recovered from the viral infection.

Acknowledgement

This work is supported by the grant of the Government of the Russian Federation for the state support of scientific research carried out under the supervision of leading scientists, agreement 14.W03.31.0009.

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