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EDITORIAL

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COVID-19: Some clinical questions after the first 4 months

Coronavirus disease 2019 (COVID-19) is a multiorgan disease with multiple faces and clinical features. Most patients present with none or only mild symptoms, but severe presentations with need for mechanical ventilation and high case fatality may be observed.[1-3]

The clinical presentation of such severe forms is complex and essentially involves two main actors that likely participate in adversely influencing the disease progression: (a) the virus and (b) a dysregulated host response to the virus. In the last few months, particular attention has been devoted to the latter, in particular to the so-called cytokine release syndrome (CRS, characterized by an aberrant production of pro-inflammatory cytokines) that may be observed in critically ill patients with COVID-19.[4] Notably, the concomitant, intertwined presence of CRS, organ damage and cytopenia is consistent with secondary hemophagocytic lymphohistiocytosis, also known as macrophage activation syndrome.[5] It is thus little wonder that various anti-inflammatory drugs (eg tocilizumab, a recombinant humanized monoclonal antibody that inhibits membrane-bound and soluble IL-6 receptors and is approved for the treatment of patients with chimeric antigen receptor T-cell–induced severe CRS) have been proposed and are either being tested in randomized clinical trials (RCT) or used as off-label treatments in patients with severe COVID-19.[6,7] For example, this rationale guided the choice of administering tocilizumab and/or other anti-inflammatory agents in some critically ill patients with COVID-19 in some early clinical experiences, based on high level of serum IL-6, C-reactive protein (CRP), ferritin levels and/or other non-specific markers.[8,9] Although with the important limitations of residual and unmeasured confounding inherent to the observational nature of the analyses (with RCT remaining necessary to ultimately support efficacy), some groups observed a possible beneficial effect in critically ill COVID-19 patients receiving anti-inflammatory agents.[8,10-12]

Although we are in line with this vision (ie we also administered anti-inflammatory agents in selected cases[13]), we would also like to highlight two important, still unresolved questions that we encountered in our clinical practice at the bedside of critically ill patients with COVID-19 treated with anti-inflammatory agents. The first regards the role of the virus. Indeed, the fact of administering anti-inflammatory agents based on laboratory markers of exaggerated host response does not take into account possible inter-personal differences in the direct viral component of the damage. That is, we cannot exclude that an excessive anti-inflammatory effect could ultimately be detrimental in some patients, because of slowed/reduced viral clearance and delayed/impaired development of protective immunity.[4,14] From this standpoint, we feel an important additional question that will need to be answered in the near future is as to whether combinations of efficacious anti-viral agents (eg preliminary RCT results have been recently released for remdesivir[15]) and efficacious anti-inflammatory agents (if positive observational results are confirmed in RCT) could be synergistic in further improving the outcome of critically ill COVID-19 patients. Since this will mean to find a new pro-inflammatory/anti-inflammatory balance, the answer is not automatically affirmative. The second important question we would like to bring to the attention of readers is the possible effect of anti-inflammatory treatments in favouring bacterial/fungal superinfections. In general, this possibility is long-known,[16,17] and we recently provided preliminary, observational evidence that the use of anti-inflammatory agents was associated with an increased risk of developing bloodstream infections (BSI) in critically ill patients with COVID-19 in two intensive care units.[13] Notably, other commentaries have highlighted a possibly overlooked risk of superinfection in critically ill COVID-19 patients.[18,19] Again, the key term remains balance, with the accumulating observational literature (on the one hand, about possible beneficial effects of anti-inflammatory treatments, and on the other hand, about the risk of superinfection) becoming increasingly important as hypothesis-generating data to optimize the design of future RTC further investigating treatments for COVID-19 in critically ill patients. Of note, potential favourable effect of anti-inflammatory treatment (eg of low-dose steroids) to be weighed in the balance should also include a possibly reduced lung fibrotic response. In addition, the precise role of convalescent plasma therapy will also need to be further clarified, especially after non-adequately powered but still possibly positive RCT results deserving further investigation.[20]

Regarding the host, some patient-specific characteristics may strongly participate in influencing the disease

progression and outcome. In particular, elderly patients are more likely than young patients to require intensive care and to experience poor outcomes.[21-23] Of note, this is in line with what observed in previous studies conducted in patients with SARS-CoV-1 and MERS-CoV infections.[24,25] In a recent study that confirmed the trend towards poorer outcomes in elderly than young COVID-19 patients, the blood lymphocyte proportion in the elderly group was significantly lower than in the young group (19% vs 29%, $P < .001$), whereas an inverse association was observed for CRP serum levels (22.7 vs 6.49 mg/L, $P < .001$).[26] Although the reasons for the observed increased severity and poorer outcome in the elderly are still not completely clear (eg a heavier burden of baseline comorbidities may also play a key role), these laboratory alterations may suggest a role of the host inflammatory response in influencing illness severity in the elderly.[27,28] In turn, this supports the hypothesis that discrepancies in the innate and/or adaptive immune response could predispose to high morbidity and mortality also is some young patients affected by COVID-19. From this perspective, enriching our knowledge about the clinical impact of possible host genetic variations may enable an early identification of those young individuals at higher risk of dysregulated immune response and severe clinical presentation, thereby potentially improving their clinical management and outcome.[29] However, at the present time there are not yet clinical and experimental evidences supporting the routinely use of primary and secondary tests for immune system defects to define the risk of development/progression of COVID-19 in young individuals or in their families. Notably, among host factors possibly influencing the risk of either developing COVID-19 or unfavourable prognosis is also gender, with male patients having been deemed to be more at risk than women in the first clinical experiences.[30,31] Whether this difference in risk could be a proxy for differences in immune, hormonal and/or behavioural factors is under investigation. An attempt to represent the complex interplay of heterogeneous factors in predicting answers to some arising clinical questions in patients with COVID-19 is available in Figure 1.

Of course, an alternative and much more awaited strategy for preventing disease development/progression in both young and elderly individuals is vaccine development. In this regard, the dramatic spread of COVID-19 and its disrupting social and economic impact have urgently impelled over 100 pharmaceutical companies and scientific institutions to concentrate their efforts for the rapid development of safe and efficacious vaccines.[32] Notably, the current emergency situation has made it impossible to wait for the results of basic and translational studies that usually guide vaccine development and evaluation in a non-pandemic context.[33] However, the combination of already available data for related viral family members and innovative approaches have allowed for

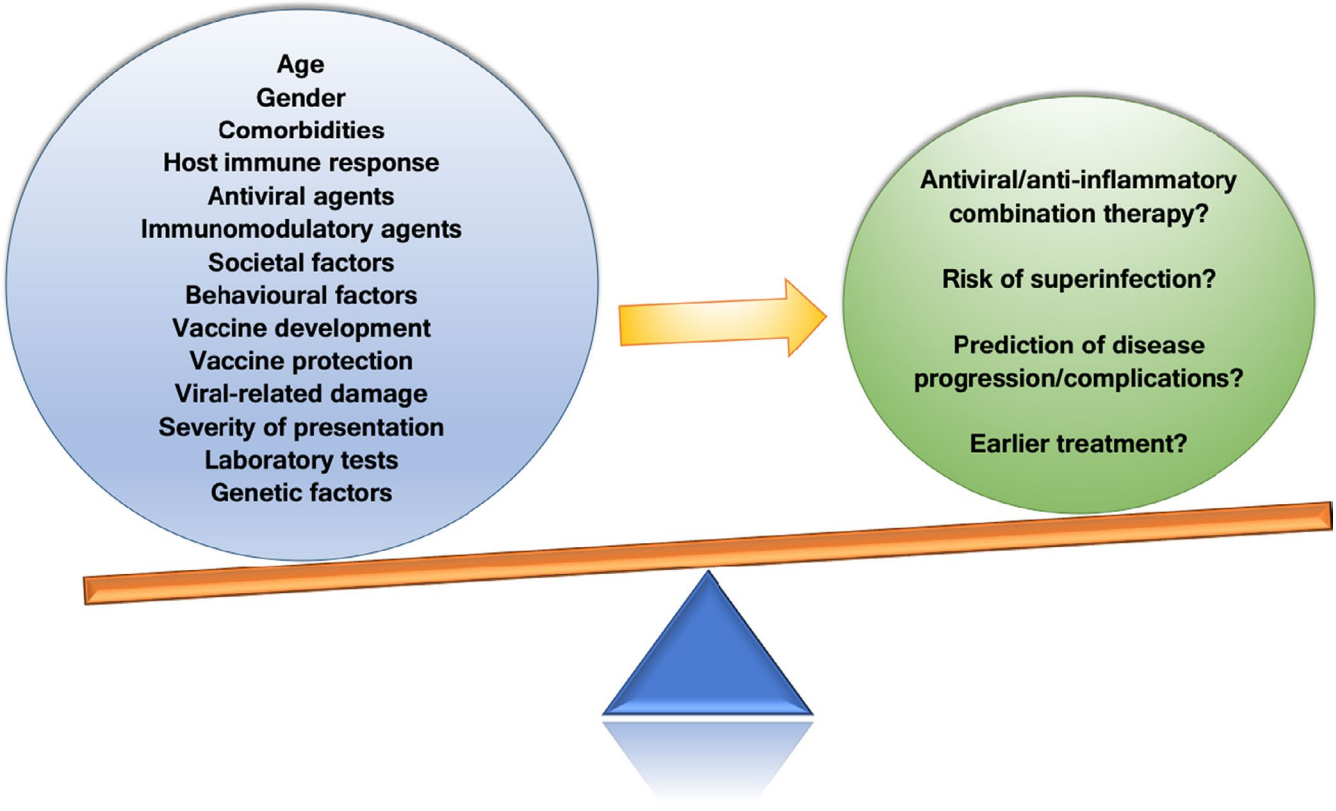

FIGURE 1 Complex interplay of host/viral/therapeutic factors in predicting answers to some arising clinical questions in patients with COVID-19

rapid identification and sequencing of SARS-CoV-2, as well as for exploiting new technologies for more rapid vaccine development.[33]

According to World Health Organization, there are at least 120 and 10 candidate vaccines in preclinical and clinical evaluation, respectively.[34] In addition to traditional inactivated and live-attenuated virus vaccines, several among SARS-CoV-2 vaccine candidates are based on new approaches, such as mRNA in lipid nanoparticles, protein subunits, virus-like particles, recombinant vectors and DNA vaccines.[35,36] As observed for other emerging pathogens, vaccine candidates are rapidly progressing through safety and immunogenicity trials, and a subgroup of vaccine candidates will be further evaluated in phase III trials.[36] Overall, there is increasing expectation that almost one of these strategies will be successful in the short term.[37] Nonetheless, many challenges remain that may delay/hamper current vaccine development: (a) the necessity to fill some knowledge gaps about effective immunity to coronaviruses; (b) the need for a careful and solid assessment of vaccines efficacy; (c) the necessity to limit/avoid any possible safety issue; and (d) the need to precisely define an effective early plan for scale-up and manufacture, owing to an expected extraordinary demand.[36]

Regarding the first point, some important questions remain about how to obtain a protective (and preferentially long-lasting) immune response. In particular, all of the following should be further investigated and better characterized: (a) the correlation between neutralizing antibodies and protection; (b) which specific epitopes to target in order to obtain protective responses; (c) the definition of a threshold for a protective, neutralizing antibody response; (d) the performance of assays commonly used in vitro for predicting protective activity in vivo; (e) the possible contribution of the respiratory tract mucosal immunity in the protection against infection or dissemination; and (f) the relevance of the contribution of T-cell responses to vaccine-mediated protection.[33]

In addition, vaccine safety needs to be guaranteed.[36] For example, a possible concern is the "disease enhancement" syndrome, which is characterized by increased infection severity or death after encountering the virus. Since this syndrome has been observed in the past for some Middle East respiratory syndrome (MERS) and SARS-CoV-1 vaccine candidates tested in animal models, there are some concerns that this could also be observed in humans immunized with SARS-CoV-2 candidate vaccines. For this reason, constant and careful monitoring of animal preclinical studies and human clinical trials in a pandemic context is and will always be required, with any possible adverse effect being carefully reported and discussed with the pertinent regulators.[38] Finally, continued cooperation among public and private institutions through government-funded and private initiatives (eg the Coalition for Epidemic Preparedness Innovations, the Bill & Melinda Gates Foundation, the Accelerating COVID-19 Therapeutic Interventions And Vaccines) remains of paramount importance both to advance vaccine development and to prevent the establishment of seasonal or additional waves of infection and disease.[36] Finally, a third preventive option would be that of waiting for the achievement of herd immunity in the absence of contention measures and vaccines, which seems not to be a good idea for several reasons.[39] Among others: (a) the expected increase in the absolute number of severe cases that may surpass the bed capacity of intensive care units, with consequent further increases in case fatality rates[6]; (b) the unacceptably high number of transmission events required to contain the diffusion, since it has been estimated that at least two-thirds of the population would need to be immune to halt the spread of the virus[40]; (c) the possibility of genetic recombination, that may eventually allow the virus to elude an initially protective immune response in the population.[41]

In conclusion, COVID-19 is a complex systemic disease, to be considered as a multiple organ dysfunction syndrome (MODS), now proposed as MODS-CoV-2. It is a serial killer with three bullets: first, lung attack, as pneumonia; second, vascular attack, as coagulation disorders with increased thrombophilia and/or haemorrhagic risk; and third, pulmonary structure remodelling leading to fibrosis.[42] We have certainly learned a lot in these first 4 months of the COVID-19 pandemic, and the unprecedented efforts of researchers around the world have certainly allowed to improve our clinical approach to COVID-19 patients. Nonetheless, 4 months are also a very short window of time, and many important challenges still remain. We should not let our guard down if we were to further understand and effectively counteract both the spread and the worrisome clinical, societal and economic impacts of SARS-CoV-2.

CONFLICT OF INTEREST

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