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Editorial

Urgent avenues in the treatment of COVID-19: Targeting downstream inflammation to prevent catastrophic syndrome

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ARTICLE INFO

1. Introduction

At present, healthcare systems all over the world are coping with the new coronavirus infection [1]. In particular, tremendous efforts are being made in order to support governments in the policy of infection spread containment and early detection, and researchers are working on causal treatment and the treatment of the severe and critical manifestations downstream from the viral infection [2]. As largely known, coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with droplets and contact as the main way of transmission. Since the first case reported in Wuhan, China, in December 2019, the outbreak has gradually spread nationwide and then abroad, rapidly becoming a pandemic infection. Now, coronaviruses (CoVs) have come back into the limelight after the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East Respiratory Syndrome (MERS-CoV) outbreak in Saudi Arabia and South Korea.

The Rheumatology scientific community has been involved in the management of this pandemic infection, since some treatments, usually employed in patients with inflammatory rheumatic diseases, might be useful to directly counteract the virus, as suggested for antimalarials [3], and more recently for baricitinib, or be effective in downregulating the dangerous inflammatory pathways triggered by the virus itself [4]. A first and crucial issue to address is whether and when it is important to target the viral infection or the downstream inflammatory events as a priority for clinical purposes. Our past experience in hepatitis C virus infection (HCV) and cryoglobulinemic vasculitis (i.e., an autoimmune and lymphoproliferative disease driven by a treatable infection) may be of value to this end, as it shows that, for life-threatening and severe disease manifestations, the immediate targeting of the events downstream of infection is mandatory [5]. Currently, the humanized monoclonal antibody anti-interleukin-6 receptor (anti-IL-6R), namely tocilizumab, appears as a promising tool to turn off the cytokine storm, which dramatically complicates the course of the infection in some patients, causing a rapidly fatal acute respiratory distress syndrome. The rationale for the use of anti-cytokine drugs is to play for time, by decreasing the dangerous inflammatory peak, while the immune system is building the adaptive response to the virus. As we write this paper, several protocols using anti-IL6R treatments are starting to recruit COVID-19 patients in different countries to build an evidence-based support for this treatment. Tocilizumab is an effective and safe treatment for rheumatoid arthritis, for systemic and polyarticular juvenile chronic arthritis and for the most frequent systemic vasculitis in adults, i.e., giant-cell arteritis. Moreover, it has been recently licensed for the treatment of cytokine storm syndrome in CAR-T protocols [6]. Interleukin-1 (IL-1) is another proinflammatory cytokine involved in the early phases of cytokine release syndrome and clinical protocols involving IL-1 blockade are being adopted in several countries.

A second important open and urgent question is, however, at which stage of the infection this treatment approach has to be best applied. To answer this question, it is important to carefully consider what we already know about coronaviruses from the lessons of previous epidemic infections, and to compare with COVID-19 outbreak.

2. Clinical comparisons

In the 2003 SARS-CoV outbreak, patients complained of high fever, myalgia, dry cough, and lymphopenia as the most characteristic symptoms or signs. In about one third of the cases, patients also developed an atypical pneumonia, with acute respiratory distress as result of extensive acute lung damage [7]. These characteristics are very similar to those registered in the current outbreak [8], where, after first systemic symptoms, dyspnoea is estimated to arise in a median of 5 days (IQR, 1–10), hospital admission occurs after 7 days, and ARDS after 8 days (IQR, 6–12 [8]. Importantly, SARS-CoV patients admitted to the Intensive Care Unit showed higher white blood cell and neutrophil counts, as well as higher levels of D-dimer, creatine kinase, and creatine, emphasizing the role of the systemic inflammation downstream the virus infection, and the transformation of the infectious disease into a systemic immunological and inflammatory disease. Indeed, in nonsurvivors, all these laboratory findings were much more pronounced. As seen in the ongoing coronavirus outbreak, also in the 2003 SARS-CoV outbreak, several factors including advanced age, male sex, comorbidity, high levels of lactate dehydrogenase and creatine

kinase, and high initial absolute neutrophil count, were significant predictive factors for intensive care unit admission and death [7].

3. Tissue involvement

Lung pathology in 2003 SARS-CoV patients showed epithelial cell proliferation and desquamation, hyaline membranes formation along alveolar walls and cells infiltration (lymphocytes, neutrophils, and monocytes) during the early stage of the disease, while, of note, increased fibrosis and multinucleated epithelial giant cells formation at a later stage, highlighting the existence of a two-phase lung injury. A first acute phase with diffuse alveolar inflammation, was followed by more organized inflammation, but also permanent secondary damage [9]. Furthermore, patients still manifested lung injury at a time when the viral load was falling, supporting the immune nature of the lung damage possibly independent from infection. Interestingly, the lungs from actual coronavirus pneumonia patients showed alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation and hyaline membrane formation. Most of the infiltrating lymphocytes, i.e., the major cellular component of lung inflammation, were CD4-positive T cells, attracted into the lungs from the peripheral blood, which contributed to the progressive peripheral blood lymphopenia. Pulmonary interstitial fibrosis was also observed. In addition, inflammation and damage of the heart, vessels, liver, kidney and other organs were evident indicating a widespread diffusion of the virus leading to multiorgan localization of downstream pathogenetic events [10]. Thus, coronavirus infection can turn into an inflammatory immune systemic disease, with clinical and subclinical simultaneous involvement of many organs.

4. Cytokine profile

In general, the cytokine profile of SARS patients showed a marked elevation of the Th1 cytokine interferon (IFN)-gamma, of inflammatory cytokines interleukin (IL)-1, IL-6 and IL-12 for at least 2 weeks after disease onset. The chemokine profile demonstrated significant elevation of neutrophil chemokine IL-8, monocyte chemoattractant protein-1 (MCP-1), and Th1 chemokine IFN-gamma-inducible protein-10 (IP-10) [11]. Of note, levels of some pro-inflammatory cytokines including MCP-1, TGF-β1, TNF-alpha, IL-1beta, and IL-6 in autopsy tissues from four patients who died of SARS were expressed in the SARS-CoV-infected ACE2+ cells. Furthermore, SARS-CoV 3a protein activates the NLRP3 inflammasome in lipopolysaccharide-primed macrophages [12]. Consistently, in the murine model of CAR T cell-induced cytokine release, the severity is not mediated by CAR T cell-derived cytokines, but by IL-6, IL-1 and nitric oxide (NO) produced by recipient macrophages [13]. IL-6 signalling can be targeted by tocilizumab and sarilumab (a human monoclonal antibody that targets IL-6 receptor with higher affinity than tocilizumab). Currently used drugs to target Il-1 are anakinra (an IL-1 receptor antagonist) and canakinumab (a human monoclonal antibody that binds IL-1β). Importantly, they proved effective in autoinflammatory diseases, and also in macrophage activation syndrome, which rarely complicates the course of autoinflammatory diseases; there is then a strong rationale for their use in SARS patients.

When dealing with the antiviral response, it was already shown in 2003 that the early immunological responders (PCR-positive/antibody-positive for the virus) had a higher serum interferon-gamma profile if compared to late immunological responders (PCR-positive/antibody-negative [14]. In addition, late immunological responders tended to have higher levels of IL-6 and of IL-8. Coronaviruses try to escape the innate immune system, the first-line of the human immunological response, by lowering the interferon response and, in this way, they buy time to replicate and undisturbedly spread in the body. In predisposed individuals (e.g., late responders) the immunological inflammatory response may acquire the characteristics of the cytokine storm syndrome, now seen also in some COVID-19 patients. Overall, this subset of COVID-19 patients should be identified early, and higher IL-6, lower lymphocyte count, and higher neutrophil count, and late seroconversion might be useful biomarkers. Also, some chemokines, i.e., IP-10 (CXCL10), may be involved. It is also not surprising that older and male patients with weaker interferon-derived immune response are mostly represented in this subset.

It has recently been suggested that baricitinib, a Janus Kinase 1 selective inhibitor, may be useful in COVID-19 severe respiratory disesase [15]. As baricitinib inhibits AP2-associated protein kinase 1 (AAK1) it may reduce receptor mediated endocytosis of the virus in target cells. Moreover, by interfering with downstream signalling of numerous cytokines like IL-6 it may also prevent subsequent cytokine release syndrome. However, JAK 1 inhibition also interferes with interferon signalling, which should probably be preserved in the early phases of the disease. Thus, the balance between advantageous and deleterious effects should be pondered and, the correct time frame for the use of baricitinib be clearly defined.

5. Complement activation

More recently, several studies have focused on complement activation in SARS-CoV patients and animal models, where increased serum and lung complement cleavage products were observed. Mice deficient in C3 are protected from SARS-CoV-induced lung pathology, improve in respiratory function, and show lower levels of inflammatory cytokines/chemokines in the lung and serum [16,17]. Indeed, inhibition of complement activation alleviates acute lung injury induced by highly pathogenic avian influenza H5N1 virus infection [18]. Treatments targeting complement activation with humanized anti-C5a antibody greatly reduce lung histopathologic injury and inflammation in a monkey model of virus-induced (H7N9) acute lung injury [18].

Overall, there is a rationale also for targeting complement activation in COVID-19 patients, and a humanized monoclonal antibody anti-C5a, namely eculizumab, currently registered for paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, myasthenia gravis, and neuromyelitis optica spectrum disorder, and already effectively off-label applied in catastrophic antiphospholipid syndrome, might potentially be useful in this setting.

6. Lung damage and fibrosis

Although this does not represent the current clinical priority, it may be convenient to begin thinking of managing patients also beyond the acute phase. Lung fibrosis followed SARS-CoV infection in some patients, and this disabling consequence should be prevented, if possible [19]. Consistently, serum TGF-β, which induced proliferation of fibroblasts, is overexpressed at the late stage of coronavirus infection [14]. It is known that TGF-β is an anti-inflammatory cytokine that can induce fibrogenesis. More recently, it has been suggested that pulmonary fibrosis in SARS-CoV is caused by a hyperactive host response to lung injury mediated by epidermal growth factor receptor (EGFR) signalling [20]. Inhibiting EGFR signalling, by the use of tyrosine kinase inhibitors like nintedanib, a drug licensed for idiopathic lung fibrosis, seems promising for interstitial lung disease in systemic sclerosis [21], and might also be useful for COVID-19.

7. Targeting for treatment

COVID-19 is now a huge challenge for health systems worldwide. It has spanned the globe, now exceeding hundreds of thousands of cases and tens of thousands of deaths, and different treatment approaches are currently been investigated. The present Chinese and Italian experience along with the past history of SARS-CoV have taught us that people with weaker immune response, in particular the elderly with comorbidity, can develop an abnormal uncontrolled inflammatory response with acute and diffuse lung damage, often leading to death.

We herein provide the following messages supported by the long-term clinical experience and scientific approach by rheumatologists and immunologists, and also by studies in virus-mediated autoimmune disease when the issue of targeting infection and/or downstream events was crucial. These should be of value to integrate the scientific evidence in COVID-19. First, giving priority to targeting the inflammatory response to the COVID19 infection appears more feasible in some patient subsets, seemingly the more severe ones, when disease has already evolved, and likely also for those in earlier stages, but at higher risk. Secondly, when available, concomitant etiological, antiviral therapy remains in any case a cornerstone in all patients. Immunosuppressant can make the viral clearance more difficult, and an antiviral therapy should be combined when an immunosuppressant is given, in the absence of additional data at present. Thirdly, besides IL-6 pathways blockers, other biologic drugs currently used by rheumatologists may be employed in selected patients. In our opinion, targeting IL1 and complement activation have a strong rationale. These are assumptions and we should keep in mind also the deleterious effect of TNF-α blockade in septic shock. This means that we should be careful and rigorous in the evaluation of these new possibilities. Finally, possible long-term sequelae, mainly lung fibrosis, should be kept in mind, monitored, and possibly treated and prevented in the near future.

As countries try to buy time to save their health system from collapse through contagion containment policies, individual patients must also be helped to save time for the immune system to react effectively to the virus.

Disclosure of interest

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