REVIEW ARTICLE

Dysregulation of the immune system as a driver of the critical course of novel coronavirus disease 2019

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KEY WORDS

clinical course, coronavirus disease 2019, cytokine storm, hyperinflammation, severe acute respiratory syndrome coronavirus 2

ABSTRACT

Novel coronavirus disease 2019 (COVID-19) is a highly contagious, respiratory disease caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Given that inflammatory immune cells may induce severe lung injury, the involvement of immunological factors in the pathogenesis of the disease cannot be overestimated. It has been demonstrated that coronaviruses have developed mechanisms of immune evasion, making themselves invisible to the immune system at an early stage of infection. The mechanism relies on inhibiting the antiviral response of type I interferons, which enhances uncontrolled viral replication in epithelial cells. There has been a growing body of evidence showing that fatal hyperinflammation (cytokine storm) responsible for the severe course of COVID-19 is a consequence of massive SARS-CoV-2 replication rather than inappropriate hyperresponsiveness of the immune system. Therefore, the suppressed antiviral innate immune response seems to be the primary cause of the delayed critical cascade of uncontrolled immune events leading to fulminant systemic inflammation. The occurrence of virus transmission even in asymptomatic individuals infected with SARS-CoV-2 clearly strengthens the evidence for the key role played by the sufficient immune control of viral replication in a subset of cases (eg, in children, a population with a highly effective innate immune response). Although administration of immunomodulatory drugs is recommended under certain conditions by the guidelines for COVID-19 management, controversies regarding treatment protocols in immunocompromised patients infected with SARS-CoV-2 still exist. Extending clinicians' knowledge on the dysregulated immune response, which is a driver of the COVID-19 outcome, may improve both therapeutic strategies and the prognosis of patients infected with SARS-CoV-2.

Introduction At the end of 2019, we observed an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which causes a respiratory disease called coronavirus disease 2019 (COVID-19). Coronaviruses are enveloped, positive-stranded RNA viruses belonging to the Coronaviridae family.[1] It has been found that SARS-CoV-2 can be transmitted from human to human through respiratory droplets or close contact.[2] The rapid spread of the virus caused by the highly contagious nature of the virus and a relatively high proportion of asymptomatic infected individuals led to the uncontrolled transmission of SARS-CoV-2, resulting in a pandemic in March 2020, which is still ongoing.[3] Whole-genome sequencing of viral RNA has shown that the virus causing COVID-19 demonstrates a highly similar gene composition to that of SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[4] An envelope-anchored spike protein promotes entry of the virus into the host cell by binding to a host receptor and then fusing viral and host cell membranes.[1] Liu et al[5] reported that angiotensin-converting enzyme 2 (ACE2) is probably used by the structural spike protein of SARS-CoV-2 as a receptor similar to that of SARS-CoV.

The site of initial infection with SARS-CoV-2 is unknown. However, it is currently thought to be a respiratory tract infection. The aerosolized uptake of SARS-CoV-2 promotes infection of ACE2-expressing target cells, such as type 2 alveolar

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cells, a relatively small subset of cells in the lungs, although other receptors and entry modes may also be used in COVID-19.[6] Moreover, in the light of several reports showing heterogeneous clinical manifestations of the first symptoms, such as dyspnea, diarrhea, acute cardiac injury, or kidney failure, other target cells may exist.[7,8] Using single-cell RNA sequencing data analyses of ACE2 receptor expression, Zhou et al[8] identified organs including the lungs, heart, esophagus, ileum, kidneys, and bladder as vulnerable to SARS-CoV-2 infection. Recent reports have shown that 80% of individuals infected with SARS-CoV-2 may be asymptomatic, thus being carriers of the virus capable of infecting others. Current symptoms reported in patients with COVID-19 include mild-to-severe respiratory disease accompanied by fever, fatigue, dry cough, myalgia, and difficulty breathing.[9]

Immunopathology of coronavirus infection The fact that the SARS-CoV-2 genome is closely related to that of SARS-CoV and MERS-CoV as well as the accumulated clinical and experimental data on coronavirus infections allow us to hypothesize how the interaction between the host's immune response and SARS-CoV-2 looks like. In fact, the immunopathogenesis of COVID-19 appears to be clearly associated with a dysregulated immune response, which may result in increased viral replication and lung damage in a proportion of cases. Histopathology of pulmonary lesions in patients with SARS demonstrated nonspecific inflammatory responses, such as edema and inflammatory cell infiltration, leading to pulmonary tissue damage with subsequent hyperplasia and fibrosis.[10,11] Therefore, understanding the immunological background of SARS-CoV-2-mediated infection would help to design an appropriate immunological treatment method and prophylactic vaccines against SARS-CoV-2.

Innate immune response The first line of the immune response to viruses involves innate immune cells, such as neutrophils and/or macrophages. An effective innate immune response against viral infection relies on the reaction of type I interferons stimulating natural killer cells and macrophages to elicit antiviral activity. Therefore, type I interferons play a crucial role in controlling viral replication and inducing an effective adaptive immune response by presenting viral epitopes to lymphocytes. Successful initiation of type I interferon response should be capable of suppressing viral replication and dissemination at an early stage of infection with coronaviruses.[12] Remarkably, coronaviruses appear to be adapted to evade the immune detection and surveillance system, and have a high potential to dampen the host's immune response. The longer incubation period of coronaviruses compared with influenza virus clearly supports this hypothesis (2–14 days versus 1–4 days, respectively).[13] The mechanism of immune evasion shown by coronaviruses relies on the suppression of the innate immune response, primarily type I interferons, while inducing a delayed proinflammatory response in lung epithelial cells,[14] and, moreover, this attenuation is correlated with disease severity.[15] Markedly, a decreased secretion of interferon β (belonging to type I interferons), tumor necrosis factor α (TNF-α), and interferon γ–inducible protein 10 (IP-10) has been observed in coronavirus infections. It may lead to an impaired recruitment of innate cells into inflamed tissue at an early stage and facilitate uncontrolled viral replication.[14] This early and overwhelming viral replication contributes, in turn, to a delayed release of high amounts of cytokines, the vast majority of which is proinflammatory and, thus, activates and recruits immune cells to the site of inflammation.[16] These immune cells exert their function by killing virus-infected pulmonary cells and inducing the adaptive cellular and humoral immune response. As a consequence, patients infected with coronaviruses, including SARS-CoV-2, exhibit high levels of inflammatory cytokines, such as interleukin 1β (IL-1β), IL-2, IL-6, IL-8, IP-10, macrophage inflammatory protein 1α (MIP-1 α), and TNF-α, involved in lung tissue damage. A proportion of them develop severe pneumonia or acute respiratory distress syndrome (ARDS), lethal for half of cases requiring intensive care.[14,17] The hypothesis of cytokine dysregulation, called cytokine storm, in the pathogenesis of coronavirus infections has been confirmed in several reports.[16]

Of note, viral transmission may occur even in asymptomatic subjects infected with SARS-CoV-2, which suggests a sufficient immune control of viral replication, usually seen in children, a population with highly effective mechanisms of innate immune response. Therefore, the innate immune response in SARS-CoV-2 infection may play a major role in protective or destructive responses, and certain immune interventions can improve innate immunity. Consequently, antagonists of some proinflammatory cytokines, antiviral agents, and type I interferons are currently under clinical investigation.[14] However, it should be strongly emphasized that the timing of administration of these interventions seems to be crucial to yield a protective response.[14] Therefore, it is necessary to search for circulating factors (easy to detect and measure) predictive of the clinical course and outcome of SARS-CoV-2 infection.

Adaptive immune response The microenvironment generated by cytokines released during innate immune responses drives differentiation of lymphocytes towards effector and/or regulatory cells. There are a few studies demonstrating the role of T cell responses in coronavirus infection.[18,19] The profound cytokine alterations during coronavirus infection are usually accompanied by lymphopenia, primarily in critically ill patients.[19] In line with this, elevated TNF-α and IL-6 levels have been found to

negatively correlate with the total number of T cells, both $CD4^+$ and $CD8^+$, which may affect the clinical course of COVID-19.[19] The number of $CD8^+$ T cells in the pulmonary interstitium is of high importance for clearance of coronaviruses by inducing immune-mediated injury.[11] It has been demonstrated that $CD8^+$ T cells account for about 80% of infiltrating inflammatory cells in the pulmonary interstitium of patients infected with SARS-CoV. The intensity of highly toxic $CD8^+$ T cell infiltration and function may affect pulmonary tissue.[20] In contrast, a strong downregulation of $CD8^+$ T cells in several cases may promote insufficient viral clearance.[21] In turn, $CD4^+$ T cells appear to be of great relevance for coronavirus immunopathology, since these cells drive the effector immune response by inducing maturation of B cells and activating macrophages and cytotoxic $CD8^+$ T cells. Remarkably, $CD4^+$ T cells can also produce proinflammatory cytokines depending on their differentiation, such as IL-2, interferon γ (Th1 cells), and IL-17 (Th17 cells). The IL-17 cytokine recruits monocytes and neutrophils to the sites of inflammation, thus enhancing inflammation by inducing the secretion of other proinflammatory factors, such as IL-1β, IL-6, IL-8, IL-21, TNF-α, and monocyte chemoattractant protein 1. Regarding $CD4^+$ T cell alterations, coronavirus infections seem to be related to T cell exhaustion and skewing the immune response toward the immunosuppressive Th2 type, depending on disease severity.[17] In contrast, the Th1 response has been found to be predominant in the recovery phase of coronavirus infection, indicating that appropriate Th1 cell function might control the clinical course of SARS, MERS, and probably COVID-19.[22] In general, the Th1 response has been proven to play a crucial role in adaptive immunity to viral infections. The $CD4^+$ T cell population also contains a subpopulation exerting a regulatory function, known as regulatory T cells (Tregs). However, little is known about the role of Tregs in patients infected with SARS-CoV-2.

It has been emphasized that T cell responses correlate with the level of neutralizing antibodies specific for SARS-CoV epitopes.[22] The production of neutralizing antibodies by plasmocytes, which are highly differentiated B cells, plays a protective role by limiting inflammation at a later phase of viral infection, and the appropriate titers of specific antibodies may prevent reinfection.[23] Severe acute respiratory syndrome coronavirus induces seroconversion between 4 to 14 days after disease onset, and in MERS-CoV infection even later—after 14 to 21 days.[24] Specific immunoglobulin G (IgG) antibodies isolated from patients after MERS-CoV or SARS-CoV infection are maintained during recovery and convalescence. It has been reported that a delayed and weaker humoral response is a predictor of the severe outcome of SARS and MERS.[25] So far, little is known about the serological response in SARS-CoV-2 infection.[23,26] Zhou et al[26] showed a specific IgM peak at day 9, switching to IgG by week 2. Of note, they confirmed the SARS-CoV-2-neutralizing capacity of sera obtained from COVID-19 patients in vitro and the crossreactivity with SARS-CoV as well. There is still no evidence on antibody titers or kinetics in patients with a critical outcome of COVID-19. Based on the available literature on COVID-19, the T cell response seems to be of great clinical importance in the acute phase of infection, while humoral activity may play a role in the recovery phase[23] and might be used for prophylaxis and treatment by constructing an anti–SARS-CoV-2 vaccine, but this requires further research.[27] Altogether, during severe coronavirus infection, the abnormal function of both innate and adaptive immune responses is observed, which may lead to uncontrolled viral replication and/or immune-mediated tissue damage.

Dysregulated immunity in coronavirus disease 2019

Data on immune response dysregulation in patients with COVID-19 are still scarce. In fact, there are only 2 reports on phenotyping the immune cells regarded to be involved in the pathogenesis of COVID-19.[23,28] Qin et al[28] showed decreased B and natural killer cell counts and indicated a subpopulation of T cells with nonaffected function. Although a decrease in both $CD4^+$ and $CD8^+$ cell counts was observed in all patients, the deletion of the $CD4^+$ subset was more pronounced in severe COVID-19 cases only. The authors also reported dysregulation in regulatory T cell subsets, observing an increased activity of $CD8^+CD28^-$ suppressor T cells and a decreased activity of $CD4^+CD25^+CD127^-$ regulatory T cells, primarily in severe disease. That study showed that immune impairment is associated with the T cell compartment, which suggests the usefulness of T cell subset evaluation in the early diagnostic workup of critical disease.[28] Meanwhile, the kinetics of immune responses in relation to the clinical and virological characteristics of a patient with mild-to-moderate COVID-19 requiring hospitalization were presented in a recent case report.[23] The observation of the recovery phase of SARS-CoV-2 infection revealed that its resolution was associated with a clear induction of humoral response and T cell–related support to B cells, whereas the viral-specific T cell acute response declined with resolution.[23] That study was limited by the fact that it was based on a short-term follow-up of a single patient with symptomatic yet nonsevere disease and lacked a detailed analysis of specific proinflammatory (Th1 and Th17) and regulatory (Th2 and Treg) subsets of T cell responses. In addition, there was no information on the frequency of specific subsets of monocytes or macrophages showing a potential to be involved in the immunopathogenesis of COVID-19. Nevertheless, the 2 studies performed in patients with COVID-19 provided a general view of the involvement of immune responses in SARS-CoV-2 infection and further research is needed in this field.

Cytokine storm syndrome: the result of a maladjusted immune response The majority of patients infected with SARS-CoV-2 remain asymptomatic or develop mild symptoms. However, up to 20% of patients, primarily older and with comorbidities, develop severe disease with interstitial pneumonia and/or ARDS, requiring respiratory support and intensive care as a result of the uncontrolled cytokine release.[29] There has been a body of evidence showing that profound immune dysregulation, including cytokine storm, may lead to the progression of COVID-19 to critical disease. Understanding the underlying mechanisms of these immunological alterations may contribute to identifying the most effective treatment, which is currently an urgent issue of debate.

Regarding the clinical manifestations of cytokine storm syndrome in COVID-19, it should be emphasized that, apart from ARDS, this critical cytokine dysregulation may also lead to septic shock in a subset of patients with COVID-19, characterized by elevated concentrations of acute phase factors and macrophage activation syndrome, including hepatic dysfunction with hyperferritinemia and diffuse intravascular coagulation.[17] Also, some patients with COVID-19 develop secondary hemophagocytic lymphohistiocytosis, which is a virus-driven hyperinflammatory syndrome characterized by fulminating hypercytokinemia with multiorgan failure, including ARDS in 50% of cases.[30,31] This fatal, cytokine-induced syndrome is thought to be under-recognized during viral infection and occurs in a relatively small proportion of patients with sepsis (about 4% to 5%). Notably, the cytokine profile is similar to that observed in severe COVID-19.[17] Of note, the common feature of the above critical states is uncontrolled release of inflammatory cytokines, of which IL-6 appears to play a key role in COVID-19-related cytokine dysregulation.

However, there are still several unaddressed issues regarding the cytokine storm. What is the reason for such a massive proinflammatory cytokine release during COVID-19 progression? We cannot exclude that, in spite of high exposure to the virus and high viral load of epithelial cells leading to increased tissue damage, the compromised mechanisms of the innate immune response should be considered a significant cause of the cytokine storm. The hypothesis of cytokine dysregulation in the pathogenesis of coronavirus infections has been confirmed by several reports,[32] which documented the diminished levels of antiviral cytokines, such as type I interferons, usually secreted at a very early stage of viral infection.[33] Lack of type I interferons has been shown to affect the Th1 cell response, favoring Th2 type immunity, which, in turn, has been found to be associated with an unfavorable outcome of COVID-19.[17] Most importantly, the attenuated antiviral innate immune response may lead to uncontrolled virus replication, which, subsequently, induces a delayed, strong inflammatory response. Patients infected with SARS-CoV-2 exhibit high levels of proinflammatory cytokines and chemokines (IL-1β, IL-2, IL-6, IL-8, IP-10, MIP-1A, and TNF-α). It has been reported that infected pulmonary epithelial cells and activated immune cells infiltrating the site of inflammation become a reservoir of inflammatory mediators. However, some levels of these cytokines are extremely elevated mainly in patients with critical COVID-19, in whom they lead to plasma leakage, vascular permeability, and disseminated intravascular coagulation.[17] Interleukin 6 and other hyperinflammatory indices have been reported to be highly upregulated in 76% of patients with severe COVID-19 compared with 30% of those with mild disease.[34] Therefore, an inhibitor of the IL-6 receptor (tocilizumab), as an attenuator of the cytokine storm, interstitial pneumonia, and fibrosis, is recommended in guidelines on the treatment of severe COVID-19 in patients with hyperinflammation and/or respiratory failure.[35-37]

Although it is still a subject of investigation, some explanations for this phenomenon have been proposed. For instance, a high rate of rapid apoptosis of virus-infected epithelial cells (called pyroptosis) in the respiratory tract, caused by massive viral replication, may prompt a vast release of cytokines and induce a cytokine storm, hence recruiting and activating other mediators of inflammation.[38] Another possibility is the antibody-dependent enhancement of SARS-CoV-2 due to prior exposure to other viruses or the same virus expressing similar antigenic epitopes. It modulates the immune response to the current infection (or reinfection occurring shortly after the first one) and can elicit a cytokine storm, enhanced inflammation in the lungs, and lymphopenia observed in the majority of severe cases or deaths.[39] A candidate epitope capable of promoting antibody-dependent enhancement has been proposed, namely, a spike protein—a common structural protein found in SARS-CoV and SARS-CoV-2, inducing specific anti–spike protein IgG antibodies as promoters of proinflammatory macrophage accumulation and activation in the lungs.[38] Recently, an increased release of neutrophil extracellular traps (NETs) from activated neutrophils has also been proposed to be involved in fulminant hyperinflammation and thrombosis, severely complicating the clinical course of COVID-19.[40-44]

Neutrophil activity and NETosis as mediators of the aggravated thrombotic-inflammatory state in coronavirus disease 2019 Considering transepithelial neutrophil migration and intensive epithelial alveolar disruption in acute lung injury and ARDS in severe patients with SARS,[41] the role of neutrophil activity and NETosis in the COVID-19-related cytokine storm appears to be of clinical significance as well. One of the diagnostic characteristics of COVID-19 pneumonia is an elevated neutrophil count, and growing data have shown that it might be even an early indicator of the adverse

clinical course of SARS-CoV-2 infection.[45] In fact, a highly increased neutrophil-to-lymphocyte ratio has been reported in critically ill patients.[45] Like macrophages, neutrophils are important players in innate immunity, constituting the first line of defense against pathogens, including viruses. It has been demonstrated that these activated cells have the capacity to release NETs, which attenuate infection by trapping and killing pathogens.[42,46] NETosis is considered to be a type of programmed cell death distinct from apoptosis and necrosis.

Neutrophil extracellular traps are extracellular webs of chromatin and microbicidal proteins (including neutrophil elastase and myeloperoxidase) as well as histones and oxidant enzymes, exerting intrinsic proinflammatory properties.[46] Due to cytotoxic activity, NETs prevent the spread of pathogens and facilitate the accumulation of antimicrobial factors at the site of inflammation.[42,46] However, when not sufficiently controlled, NETs may exhibit the capacity to propagate inflammation and microvascular thrombosis, thus contributing to progression from viral pneumonia to ARDS or multiorgan failure.[47] Accordingly, in patients with severe COVID-19, elevated NETosis markers have been found to be associated with acute phase indicators, such as C-reactive protein, lactate dehydrogenase, neutrophil count, platelet count, and D-dimer levels, the latter indicating hyperactivity of the coagulation system.[40] Therefore, the role of NETs in thrombosis and, what is more relevant for COVID-19, in microvascular thrombosis, is increasingly appreciated. In fact, recent data have reported the occurrence of several thrombotic complications of severe COVID-19 (both venous and arterial).[48]

The triggers of NETosis in COVID-19 are still under investigation. However, a certain role may be assigned to virus-damaged epithelial cells, activated platelets, or high amounts of inflammatory cytokines, mainly IL-1β and IL-6.[49] The impact of inflammatory cytokines on the release of NETs appears to be highly relevant, given that sera from COVID-19 patients are stimulators of NETosis, when added to control neutrophils.[40] Based on the preliminary data on the involvement of NETs in the pathology of COVID-19, one can speculate that increased NETosis in severe cases of COVID-19 may act bidirectionally: not only by mechanical entrapment of the virus, but also by triggering and aggravating a thrombotic--inflammatory storm.[40]

Given the urgent need to develop effective treatment protocols, further studies assessing the effect of COVID-19-related NETosis inhibitors on clinical complications are warranted. A recent clinical study on the use of dipyridamole, an adenosine receptor agonist potent to inhibit NET formation, showed its beneficial influence on the improvement of the platelet count and D-dimer levels in severe COVID-19.[50] Also, the suppressing effect of acetylsalicylic acid and acetaminophen on NET generation in neutrophils isolated from COVID-19 patients with severe pneumonia has recently been postulated.[42]

The role of inflamm-aging in the adverse outcomes of coronavirus disease 2019 Cumulative evidence indicates that aging markedly affects immune cells,[51] which is called immunosenescence. Immune suppression has been found to correlate with age, regarding both innate and adaptive responses. However, the observation that young and middle-aged SARS-CoV-2-infected transplant recipients on immunosuppressive treatment (dampening mainly adaptive immune responses) do not develop more aggressive disease points out that an impaired innate immune response rather than the adaptive one appears to possibly play a major role in higher viral vulnerability in aged patients. Innate immune components, such as cell migration, pattern recognition receptor signaling, and type I interferon production by dendritic cells, required in response to pathogens (eg, viruses) or vaccines, have been found to impair with age. In fact, age-related innate immune downregulation may contribute to reactivation of latent viruses, such as herpes simplex virus, thus clearly indicating a diminished antiviral response in the elderly.[51] Considering that regulation between the innate antiviral response and the extent of the inflammatory response is reciprocal,[52] the age-related dampened type I interferon function and other innate immune defects supporting uncontrolled viral replication-may lead to profound cytokine dysregulation-and explain, at least in part, the much higher risk of a severe or even lethal course of COVID-19 in aged individuals.

However, apart from the affected resistance to infections, chronic subclinical inflammation, the so-called inflamm-aging, has also been observed with age, which may propagate the inflammatory response in older patients with COVID-19. Studies on macaques with SARS-CoV revealed that, despite a similar rate of viral replication in both young and old individuals, the intensity of inflammation in the lungs of the aged ones was out of control.[52] A similar relationship of inflammatory activity with age has been observed in patients with COVID-19. An unbalanced inflammatory response against SARS-CoV-2, demonstrated mainly in the elderly, prompted researchers to explore the underlying mechanisms. There is a growing body of evidence showing the role of progressive, age--related development of the proinflammatory state in older patients, mainly in those with comorbidities.[52] This progressive propensity toward a proinflammatory phenotype is a consequence of profound dysregulation of immune responses at older age, and the existing evidence points to the inability to fine-control inflammation.[53] Inflamm-aging is an immunological consequence of lifetime exposure to (a)symptomatic infections and noninfectious antigens, which are cumulatively loaded and have the ability to

persistently induce cytokine release as well as tissue damage and repair.[54] When sustained for decades, it may drive remodeling of the immune system toward a low-grade chronic proinflammatory state.

Inflamm-aging is associated with the chronic production of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α.[55] They have also been shown to be involved in the pathogenesis of most age-related disorders.[56] It has been reported that increased IL-6 levels induce C-reactive protein production in the liver, which is considered a clinical marker of inflamm-aging and regarded as a risk factor for the development of cardiovascular or other inflammatory disease.[57] Given that IL-6 is assumed to be most relevant for hyperinflammation observed in a subset of patients with COVID-19, the involvement of inflamm-aging in disease progression is strongly suggestive.

Mechanisms underlying the proinflammatory profile of the aged system are complex and involve a regressive thymic output of T cells with qualitative imbalance regarding both the reduced T cell repertoire and the limited ability to clear novel pathogens, as well as an increase in the number of T cells showing a proinflammatory phenotype.[58] Nevertheless, a shift in innate immunity toward a proinflammatory phenotype, regarding expansion of monocytes constitutively secreting IL-6, IL-1β, and TNF-α, appears to play a superior role in inflamm-aging[59] and may predispose older people to an aggravated proinflammatory response under certain conditions, such as those related to COVID-19.

Extracellular nucleic acids also have a potential to be strong inducers of innate immunity, as a consequence of an evolutionarily conserved signaling mechanism of cellular damage upon, eg, viral infection.[60] It has been demonstrated that mitochondrial DNA and telomeric DNA sequences have opposite effects on inflammatory activity: mitochondrial DNA exhibits strong proinflammatory features, while telomeric DNA exerts potent anti-inflammatory activity.[60] Considering that one of the characteristics of older people (notably those with chronic comorbidities) is shortening of telomeres,[61] it may be assumed that, the increased release of mitochondrial DNA accompanied by insufficient telomeric DNA may strongly induce and promote detrimental inflammation, described as a cytokine storm, in aged patients affected by COVID-19. Studies on the genetic background of inflamm-aging also revealed an association of sex-related genetic variants causing a higher production of IL-6 in older men, yet not in aged women,[62] which altogether may explain the higher probability of uncontrolled hyperinflammation and the adverse clinical course of SARS-CoV-2 infection in old men with pre-existing medical conditions.

Immunosuppressive treatment in coronavirus disease 2019: yin or yang? Immunosuppression in transplant recipients There is a major concern that in patients receiving immunosuppressive treatment, including organ transplant recipients and patients with autoimmune chronic inflammatory diseases, the effective suppression of immune responses with no specific antiviral therapy might result in uncontrolled SARS-CoV-2 infection and development of the severe course of COVID-19. So far, limited data are available regarding immunosuppression management in SARS-CoV-2 infection, and the results are inconsistent, primarily in transplant hosts.

It has been demonstrated that organ transplant recipients, in general, are more vulnerable to respiratory viruses, and viral infections may proceed more severely in this population, showing rapid progression to pneumonia. The prolonged clearance of viruses and development of bacterial, fungal, and other viral superinfections are usually observed in transplant hosts. The SARS-CoV-2 pandemic is still ongoing, so data on the clinical course and pattern of immune responses in immunosuppressed transplant recipients are limited. Based on own and other authors' experience, Fishman and Grossi[63] attempted to address this concern and noted that numerous transplant recipients had no contact with SARS-CoV-2-infected individuals. They manifested several common symptoms such as fever, fatigue, and dry cough at disease onset. However, other manifestations have also been observed including gastrointestinal or upper airway symptoms.[7] Leukopenia with lymphopenia, increased serum lactate dehydrogenase levels, and inconsistent upregulation of inflammatory markers have commonly been reported in recipients who developed COVID-19. Given the unknown antiviral effect of immunosuppressants used[64] and the fact that immunosuppressive therapy reduces cell-mediated immunity in order to improve immune tolerance, while prolonging the clearance of viruses and increasing the risk of infectious complications, many clinicians strongly recommend immunosuppression reduction in recipients with COVID-19 to improve viral shedding. It should, however, be emphasized that this reduction must be modest, individualized, and combined with immune modulators, such as low or modest doses of corticosteroids, statins, or IL-6 inhibitors to suppress inflammatory response aimed at maintaining the immune homeostasis.[63] Of note, the followed-up hosts exhibited renal function impairment of various degrees, increasing the risk of graft rejection following restriction in the immunosuppression regimen or, alternatively, as a result of type I interferon therapy or difficulties with monitoring the levels of calcineurin inhibitors interfering with antiviral agents used,[65] which may promote immune reconstitution. Although the clinical course of COVID-19 may vary among individual patients, a more rapid progression to ARDS and higher mortality rates have been reported in a subset of immunocompromised transplant recipients compared with immunocompetent patients.

Remarkably, a mild course and full recovery from COVID-19 pneumonia in a kidney recipient without any reduction in immunosuppression has also been reported.[44,66] Therefore, in this review, a protective role of immunosuppression in graft recipients is suggested. Consistently with this point of view, Romanelli and Mascolo[67] indicated a potentially beneficial effect of immunosuppression in transplant recipients by ascribing tacrolimus, cyclosporine, and/or mycophenolic acid (most commonly used in immunosuppressive protocols after organ transplant) a special role in the inhibition of systemic T cells, including proinflammatory Th17 cells, which are also involved in lung tissue injury in COVID-19. This theory is highly plausible; however, it does not consider the impact of innate immune cells on hyperinflammation in COVID-19. In a subset of SARS-CoV-2-related pneumonias, a significant role is attributed to virally activated, macrophage-driven cytokine storm syndrome, and not only to the hyperactivation of T cell–related immune responses. In line with this, a recent retrospective multicenter study confirmed the involvement of innate immune dysregulation and elevated IL-6 levels in the pathogenesis of lung injury in COVID-19. A clinical trial of tocilizumab (IL-6 receptor inhibitor) has recently been approved in COVID-19 pneumonia with elevated serum IL-6 levels (ChiCTR2000029 765).[17] There is a growing body of evidence showing that immunosuppression, which attenuates immune responses, is beneficial in confirmed hyperinflammation only. Therefore, all graft recipients with COVID-19 should be screened for hyperinflammation evaluated in laboratory tests to identify those in whom an immunosuppressive regimen would reduce mortality risk.

The use of corticosteroids in immunosuppressed patients remains to be the most controversial issue. Zhu et al[6] demonstrated a beneficial effect of reduced immunosuppressive treatment combined with low-dose methylprednisolone. Also, Bussalino et al[68] presented a case of full recovery from COVID-19-related pneumonia in a kidney recipient who was treated with standard immune suppression with temporarily increased doses of corticosteroids, as the patient exhibited laboratory markers of hyperinflammation with relatively stable graft function. In that patient, more intensive steroid therapy was used as an anti-inflammatory agent rather than to prevent graft rejection. Other therapeutic strategies, such as type I interferons (interferon β or inhaled interferon α), should be considered to improve the clinical course of COVID-19 in transplant recipients. In line with this suggestion are findings from a follow-up of a liver recipient, in whom a temporary immunosuppression withdrawal in combination with low doses of steroids and interferon α inhalation resulted in complete recovery from severe COVID-19 pneumonia; of note, the patient exhibited stable liver function during protocol implementation.[69]

Altogether, numerous organ recipients have recovered from COVID-19 with varying immunotherapeutic manipulations. The actual clinical characteristics of an individual recipient may strongly influence the therapeutic decision and immunotherapeutic management. For instance, comorbidities, sex differences, and the old age–related intensity of a cytokine storm may account for excess immunity and increase disease severity in some cases, hence attenuating the degree of immunosuppression reduction. Until development of a prophylactic or therapeutic vaccine and/or specific anti–SARS-CoV-2 agents, organ recipients should be closely monitored and receive individualized treatment considering the clinical course of SARS-CoV-2 infection. Moreover, clinicians need to share their experience worldwide to improve prognosis in these patients.

Immunosuppression in chronic inflammatory diseases A large group of patients who should be of particular concern during the SARS-CoV-2 epidemic comprises immunocompromised patients with chronic inflammatory diseases. These disorders include rheumatic, neurological, allergic, dermatologic, and nonspecific inflammatory bowel diseases, which are characterized by relapses. Chronic inflammation in these entities is commonly managed by immunosuppressive treatment for long-term relapse prevention. Besides the inhibitors of lymphocyte function used in organ transplantation as well (eg, azathioprine, cyclosporine, methotrexate, tacrolimus, mycophenolate, and vedolizumab), there are several biologic agents blocking proinflammatory cytokine signaling (inhibitors of Janus-activated kinases, IL-1β, IL-6, IL-12, IL-23, and TNF-α) used in the therapy of autoimmune chronic inflammation.[38] In addition, nonsteroidal anti-inflammatory agents, such as salicylates, are commonly used to control the diseases. Like in transplant recipients, there is some concern as to whether immunosuppressive treatment may increase the risk of COVID-19 complications. Based on the recent literature, we can find no strong evidence for a higher risk of SARS-CoV-2 infection or deterioration in the clinical course of COVID-19 in immunocompromised patients with inflammatory disease. At follow-up, none of the described immunocompromised patients with inflammatory bowel disease had COVID-19 symptoms or confirmed SARS-CoV-2 infection, regardless of age (including both children and adults).[70,71] Therefore, they did not require any correction of immunosuppressive treatment or dose of salicylates used. This observation concurs with previous findings from studies on SARS and MERS.[11] Also, no evidence supports reducing or discontinuing immunosuppressive therapy to lower the risk of COVID-19 in neuromyelitis optica spectrum disorders, a group of chronic inflammatory neurological entities.[72] In the light of the above reports, it cannot be excluded that

salicylates, although not tested for their potency to modify SARS-CoV-2 infection, as well as biologic agents may protect immunocompromised patients against COVID-19 complications by dampening the extent of the immune response. In fact, several biologic agents used in chronic inflammatory diseases are currently under investigation in clinical trials of patients with COVID-19, such as tocilizumab, a humanized monoclonal antibody blocking the receptor for IL-6 (NCT04317092, ChiCTR2000029765). Also, the efficacy of adalimumab, an anti–TNF-α monoclonal antibody, is being evaluated in another clinical study (ChiCTR2000030089).

Like in organ transplant hosts, corticosteroid treatment in immunocompromised patients with chronic inflammatory diseases and COVID-19 appears to be the most controversial subject of debate. In general, corticosteroid immune suppression is not routinely recommended in COVID-19-associated lung damage.[73] It has been suggested that steroids might even exacerbate pulmonary disease.[73] Several human and animal studies have shown that corticosteroid immunosuppression (both inhaled and systemic) dampens the induction of antiviral type I interferon responses to respiratory viruses,[74] thus supporting viral replication. Therefore, it is an unfavorable therapeutic strategy in cases with a high viral load and overwhelming infection. Corticosteroids and immunosuppressive drugs, such as Janus-activated kinase inhibitors (which inhibit virus cell entry, although some of them depress interferon α production as well) or cytokine inhibitors (against IL-1β, IL-6, and TNF-α), could be considered in hyperinflammation only in situations when their use is likely to be beneficial despite a higher risk of secondary bacterial infections and further clinical complications (ChiCTR2000029765). Therefore, to avoid inappropriate immunosuppressive therapy, all patients with severe COVID-19 should be distinguished based on laboratory markers of hyperinflammation to identify a subgroup in which therapy suppressing the immune response might reduce the risk of death due to a maladjusted immune response. The currently ongoing clinical trial that compares patients with COVID-19 pneumonia receiving steroids and treatment-naive controls will help us to address this concern (ChiCTR2000029386).

Based on above observations, one may surmise that fatal hyperinflammation during the course of COVID-19 is a consequence of massive SARS-CoV-2 replication rather than inappropriate hyperresponsiveness of the immune system.[75] The suppressed antiviral innate immune response seems to be the primary cause of the critical cascade of uncontrolled immune events leading to fulminating systemic inflammation. Therefore, avoiding or minimizing exposure to SARS-CoV-2 and/or strengthening the innate antiviral responses seem to be crucial for the most efficient control of SARS-CoV-2 infection.

Perspectives The SARS-CoV-2 pandemic is still ongoing, which motivates the entire medical community to share experience on an unprecedented scale. Considering that there is still neither specific treatment against SARS-CoV-2 infection nor prophylactic or therapeutic vaccine, the early identification of high-risk patients on hospital admission, in whom early application of more aggressive treatment protocols including individualized immunotherapeutic strategies—which could reduce viral load and/or improve the immune response—may bring clinical benefits and prompt disease resolution. This approach may be of clinical relevance, since the timing of these interventions has been shown to be crucial to yield a protective response in patients with COVID-19. To address this challenge, our team is currently preparing to implement a project aimed at search for immunological and genetic predictors of the critical course of COVID-19. Immunotherapeutic strategies relying on the intravenous administration of immunoglobulins collected from recovered COVID-19 patients are also currently being employed in numerous countries to neutralize SARS-CoV-2 and specifically strengthen the immune systems of newly infected patients. Immunotherapy with immunoglobulin antibodies combined with antiviral drugs might be an alternative treatment method against COVID-19, until specific vaccines are available. Nonetheless, it should be clearly emphasized that widespread vaccination against SARS-CoV-2 appears to be the most appropriate immunotherapeutic approach and the safest way to acquire herd immunity in a population.

ARTICLE INFORMATION

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