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CURRENT OPINION

Managing Cutaneous Immune-Mediated Diseases During the COVID-19 Pandemic

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Abstract

Coronavirus disease 2019 (COVID-19) is a clinical syndrome caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has spread rapidly worldwide and has been shown to have a wide spectrum of severity. COVID-19 has become a public health emergency of relevant international concern, and it was declared a pandemic by the World Health Organization on 11 March, 2020. SARS-CoV-2 infection in severe cases involves the host response as an important contributor to the disease process and tissue damage, mainly due to dysregulated and excessive innate immune responses. The primary immune response leads to viral clearance in the majority of cases. However, in a subgroup of patients, the secondary immune response may be exaggerated, leading to inflammatory-induced lung injury and other complications including pneumonitis, acute respiratory distress syndrome, respiratory failure, shock, organ failure, and potentially death. Several cutaneous immune-mediated diseases, including psoriasis, atopic dermatitis, and hidradenitis suppurativa, are therapeutically managed with biologic and non-biologic immunosuppressive and immunomodulatory drugs. The outbreak of COVID-19 affects the management of these chronic conditions, not only for those who are already receiving treatment but also for those who are about to start a new treatment to control their disease. In this article, the management of cutaneous immune-mediated diseases during the COVID-19 pandemic is discussed.

Key message

The outbreak of coronavirus disease 2019 (COVID-19) affects the management of several cutaneous immune-mediated chronic diseases, including psoriasis, atopic dermatitis, and hidradenitis suppurativa, not only for those who are already receiving treatment but also for those who are about to start a new treatment to control their disease.

The host's dysregulated and excessive innate immune response is an important contributor to the disease process and tissue damage in severe cases of severe acute respiratory syndrome coronavirus 2 infection.

Some selective immunosuppressants or immunomodulatory drugs might be useful in controlling the "cytokine storm" associated with a poor outcome of COVID-19.

Coronavirus disease 2019 (COVID-19) is a clinical syndrome caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 31 December, 2019, a cluster of pneumonia cases of unknown etiology was reported in Wuhan, Hubei Province, China. On 9 January, 2020, the China Center for Disease Control and Prevention reported a novel coronavirus as the causative agent of this outbreak. COVID-19 has spread rapidly worldwide since it was first identified in Wuhan and has been shown to have a wide spectrum of severity [1]. COVID-19 has become a public health emergency of relevant international concern, and it was declared a pandemic by the World Health Organization on 11 March, 2020; by the end of that month, more than 750,000 cases and 36,500 deaths had been reported worldwide [2].

Although COVID-19 appears to have a lower severity and mortality rate than two other previous human coronavirus (CoV) infections (SARS-CoV and MERS-CoV), a

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subgroup of patients (particularly elderly people and those with underlying medical co-morbidities) develop a severe disease characterized by interstitial pneumonia and the rapid development of acute respiratory distress syndrome or septic shock with high levels of acute-phase reactants [3, 4].

Highly pathogenic human CoV infections suppress type I interferon (IFN) production and signaling, the key component of host antiviral defense in the early phase of viral replication, thus exacerbating disease progression [5]. In line with SARS and MERS, SARS-CoV-2 infection in severe cases involves the host response as an important contributor to the disease process and tissue damage, mainly due to dysregulated and excessive innate immune responses. The primary immune response leads to viral clearance in most cases. However, for reasons that are still unclear, in a subgroup of patients, the secondary immune response may be exaggerated, leading to inflammatory-induced lung injury and complications including pneumonitis, acute respiratory distress syndrome, respiratory failure, shock, organ failure, and potentially death [6]. This exaggerated response is considered a "cytokine storm" similar to that of secondary hemophagocytic histiocytosis, which leads to an hyperinflammation state, with unremitting fever, cytopenias, hyperferritinemia, and pulmonary involvement (including acute respiratory distress syndrome) in 50% of cases [7]. The cytokine profile associated with COVID-19 is characterized by elevated serum levels of multiple cytokines [3], probably produced by highly inflammatory macrophages [8]. Interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α surge during illness and decline upon recovery; overproduction of IL-6, IL-10, soluble IL-2 receptor, and TNFα is inversely correlated with CD4+ and CD8+ T-cell counts, is associated with decreased IFN-γ expression in CD4+ cells, and correlates with the disease severity of COVID-19 [8, 9]. In severe cases, marked decreases in memory helper T cells and regulatory T cells have been observed [10].

The most commonly reported clinical symptoms of COVID-19 among approximately 14,000 cases reported to the European Surveillance System have been fever (47%), dry or productive cough (25%), sore throat (16%), general weakness (6%), and pain (5%) [1]. Diagnostic suspicion is generally made on clinical signs and symptoms (fever, fatigue, dry cough, anorexia, dyspnea, rhinorrhea, ageusia, anosmia) and confirmed by polymerase chain reaction tests on nasopharyngeal and oropharyngeal swabs or sputum. There are preliminary reports of skin involvement (erythematous rashes, widespread urticaria, and chickenpox-like vesicles) occurring in 20% of patients in the course of the disease [11]. Hospitalization, generally due to pneumonitis, occurred in 30% of cases; severe illness (requiring intensive care unit and/or respiratory support) was reported in 15% of hospitalized cases, and death in 12%. Both hospitalization and mortality rates increase steeply in patients aged 60 years and above [1].

Pulse oximetry, respiratory frequency, and chest X-ray films determine the clinical management of patients and the need for hospitalization. Multiple therapeutic approaches have been proposed and are being studied in clinical trials, including antiviral agents and hydroxychloroquine [12–14]; widespread uptake of the latter has resulted in supply restrictions for dermatologic patients with indications for antimalarials [15]. Corticosteroids are generally contraindicated in the treatment of COVID-19 [16], but the underlying cytokine storm has provided the basis for therapeutic attempts with selective immunosuppressants such as TNFα inhibitors, Janus kinase inhibitors, anti-IL-1 agents, and anti-IL-6 drugs such as tocilizumab [17, 18].

Several cutaneous immune-mediated diseases, including psoriasis, atopic dermatitis, and hidradenitis suppurativa, are therapeutically managed with biologic and non-biologic immunosuppressive and immunomodulatory drugs. The outbreak of COVID-19 affects the management of these chronic conditions, not only for those who are already receiving treatment but also for those who are about to start a new treatment to control their disease.

Most recommendations from dermatology societies [19–21], but also from other specialties that treat immune-mediated diseases (rheumatology [22] and gastroenterology [23]) recommend patients to discontinue or postpone immunosuppressive or biologic therapy in the event of COVID-19 diagnosis until the patient recovers from the infection. However, the decision to stop or withhold treatment is left to the joint consideration of the patient and physician, pondering the risk/benefit on a case-by-case basis depending on the risk of SARS-CoV-2 infection.

There is no available evidence that supports discontinuation of biologic treatment of psoriasis for most patients simply because of the risk of infection [24]. According to the results of randomized clinical trials of biological agents in psoriasis, the rates of nasopharyngitis and upper respiratory tract infections are similar to placebo [25].

Some authors have proposed a classification of immunomodulators and immunosuppressants according to "likely risk", suggesting continuation of TNFα inhibitors and anti-IL biologics ("likely moderate risk") in the presence of mild viral symptoms [26]. Other authors recommend a limitation or avoidance of ciclosporin, methotrexate, and TNFα inhibitors for dermatologic patients in areas with high infection rates and stopping all immunosuppressive and biological therapy when exposure to confirmed COVID-19 cases occurs [27]. Finally, some authors propose that the use of biologic therapies that modulate T helper (Th)-1 responses, such as TNFα inhibitors abatacept and ustekinumab, might specifically require more stringent precautions [28].

In rheumatology, poor control of rheumatoid arthritis might imply an even greater infectious risk factor than continuation of treatment [29], and the use of systemic corticosteroids might contribute to viral replication in the event of SARS-CoV-2 infection [30]. Immunosuppressive medications in transplanted patients increase the risk or duration of infections caused by viral agents, such as adenovirus, influenza, norovirus, rhinovirus, or respiratory syncytial virus [31]; the same effect does not seem to be observed for infections caused by the coronavirus family. Similarly to SARS-CoV and MERS-CoV [32], immunosuppressed status (due to transplantation, chemotherapy, or other conditions requiring immunosuppressive treatment) has not been found to be a risk factor for an adverse outcome, such as death or admission to an intensive care unit, in patients with COVID-19 compared with the general population [33]. Data from a large European center for pediatric liver transplantation located in Lombardy demonstrated that for patients in the follow-up for cirrhosis, transplantation, autoimmune liver disease, or chemotherapy for hepatoblastoma, despite some testing positive for SARS-CoV-2, none developed clinical pulmonary disease [34].

Some selective immunosuppressants or immunomodulatory drugs might be useful in controlling the "cytokine storm" associated with a poor outcome of COVID-19.

Tumor necrosis factor-α levels are moderately increased in patients with SARS, but higher levels have been observed in patients with COVID-19 and correlate with disease severity [35]. Tumor necrosis factor inhibitors might be effective in reducing SARS-CoV2 infection and the associated organ damage, by decreasing TNF-α-converting enzyme-dependent shedding of the ACE2 ectodomain, which is crucial for the penetration of SARS-CoV2 into the cell [36]. A study evaluating adalimumab in COVID-19 infection has recently been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089).

Interleukin-17 plays a crucial role in enhancing antiviral immune responses, but it may also promote and exacerbate viral illnesses, especially through antagonism of regulatory T-cell function, which is of paramount importance in viral infections of the respiratory tract [37]. An elevated Th17 response has also been observed in patients with MERS-CoV [38] and SARS-CoV [39]. In SARS-CoV-2, a Th17 response appears to contribute to the "cytokine storm", resulting in tissue damage and pulmonary edema. Extremely high numbers of CCR6þ Th17 cells in the peripheral blood of a patient with severe COVID-19 support the role of the Th17 pathway in this disease [40]. Many psoriasis treatments inhibit the IL-17 pathway directly (IL-17A and IL-17R inhibitors) and indirectly (IL-23 inhibitors). Low levels of type I IFN seem to be common to COVID-19, SARS, and MERS, and may suppress Th1 and favor Th2 responses [41], thus providing some rationale for the use of dupilumab, an IL-4/IL-13 inhibitor used in the treatment of atopic dermatitis, to mitigate the "cytokine storm" seen in some patients with COVID-19.

Baricitinib, a Janus kinase 1/2 inhibitor submitted to the US Food and Drug Administration and the European Medicines Agency for the treatment of atopic dermatitis, has been predicted to reduce the ability of the virus to infect lung cells because it targets members of the numb-associated kinase (NAK) family, including adaptor-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), which are both involved in viral endocytosis [42]. Baricitinib appears to be able to effectively inhibit AAK1 and GAK at the plasma concentration obtained with the submitted dosage for the treatment of atopic dermatitis (2–4 mg daily), as well as reducing IL-6 and IFN-γ levels, which may be responsible for the more severe forms of interstitial pneumonia due to COVID-19 [42, 43]. However, the inhibition of IFN activity and myelopoiesis might be detrimental in these patients [29].

Corticosteroids are not routinely recommended in patients with COVID-19 unless indicated for other reasons (i.e., exacerbation of asthma or chronic obstructive pulmonary disease, septic shock) because they might exacerbate COVID-19-associated lung injury, as has been the case in previous coronavirus (MERS-CoV and SARS-CoV) epidemics [44, 45]. Less information exists regarding other broad-based immunosuppressive drugs, such as cyclosporine, methotrexate, mycophenolate, and azathioprine, which are used, alone or in combination with corticosteroids, in a wide range of dermatological diseases.

In summary, the available data on past and present outbreaks of coronavirus suggest that immunosuppressed patients are not at an increased risk for severe disease and complications compared with the general population and that immunosuppressive and immunomodulatory drugs may potentially control the "cytokine storm" associated with a poorer outcome in these patients. Thus, patients with cutaneous immune-mediated diseases (including psoriasis, atopic dermatitis, and hidradenitis suppurativa) can continue their treatment even during the COVID-19 outbreak, preventing disease flares that can contribute to an increasing patient burden, disability, poor quality of life, and healthcare usage.

It is generally recommended to withhold immunosuppressive or biologic treatment in patients with active COVID-19 infection. In patients living in areas with a high incidence of the disease, especially if they develop symptoms consistent with COVID-19 or are close contacts of confirmed cases, individual consideration should be given to the lengthening of administration intervals or temporary treatment discontinuation.

Comorbidities associated with psoriasis, hidradenitis suppurativa, and atopic dermatitis (obesity, cardiovascular disease or risk factors, chronic lung disease, and asthma) and age older than 60 years worsen the prognosis of COVID-19

infection, and in these cases, treatment interruption and perhaps individual isolation in some circumstances deserve special consideration.

In the future, SARS-Cov-2 vaccination will most likely be added to the immunization recommendations for patients receiving immunosuppressive or biologic treatment for dermatologic indications, including psoriasis, atopic dermatitis, and hidradenitis suppurativa.

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Compliance with Ethical Standards

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