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Challenges in managing immunosuppressive therapies for psoriasis during the COVID-19 pandemic

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Abstract

Introduction: **During the midst of the coronavirus disease 2019 (COVID-19) pandemic, dermatologists treating psoriasis are presented with the challenge of managing immunosuppressive and immunomodulatory therapies while ensuring patient safety.**

Objective: **Here we discuss the systemic therapies for psoriasis and their implications in the context of COVID-19 pandemic, including the recommendations of leading dermatological societies and organizations.**

Discussion: **Currently, there are no definitive data regarding the impact of specific immunosuppressive and immunomodulatory therapies used for psoriasis on the natural history of COVID-19. However, the concern is that many of these medications may increase the risk of infection or prolong the clearance of the virus, although there is some ongoing speculation that some immunomodulatory therapies may actually prevent detrimental complications of coronavirus infection.**

Conclusions: **Due to the lack of evidence, we recommend that all patients on immunomodulatory and immunosuppressive therapies for psoriasis stop their treatment immediately if they are diagnosed with COVID-19 or are exposed to someone diagnosed with COVID-19. Meanwhile, until the current situation gets resolved, we recommend that the decision to continue or stop systemic treatments for psoriasis should be made on an individual basis, taking into account the patient's current progress on the treatment and the patient's concomitant risk factors for COVID-19 as outlined by the Centers for Disease Control and Prevention (CDC).**

Introduction

Psoriasis is a disorder of the immune system and has dermatologic, cardiovascular, metabolic, musculoskeletal, and neuropsychiatric consequences. Mild disease can be controlled with topical therapies, but moderate to severe disease necessitates systemic treatments that involve immunosuppression or immunomodulation[1]. Currently, we are in the midst of a global public health emergency due to the pandemic known as coronavirus disease 2019 (COVID19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)[2]. Dermatologists are presented with the challenge of managing psoriatic disease while ensuring patients retain sufficient immune capacity to protect themselves from this potentially fatal infection. The complexity of this challenge arises from the lack of empiric evidence and high-quality data regarding the pathogenic mechanisms of the virus and its interaction with host immunity, the absence of definitive treatments for COVID-19, and the concern for overwhelming the capabilities of health-care systems to care for such patients. Here we discuss systemic therapies used for psoriasis and their implications in the context of the current pandemic.

Immunosuppression and COVID-19

The precise interactions between SARS-CoV2 and the immune system remain to be elucidated. Unlike other common viral agents such as influenza, coronaviruses (including severe acute respiratory syndrome

coronavirus and middle east respiratory syndrome coronavirus) have not been shown to cause more severe disease in immunosuppressed patients[3]. The rate risk of SARS-CoV2 infection in the immunosuppressed population is unknown[4], but many other risk factors have been identified including advanced age, male sex, hypertension, obesity, diabetes, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, tobacco use, and internal malignancies[5,6]. Immunosuppressed status was not found to be a risk factor for infection or adverse outcome[5]. On the other hand, age is thought to be a risk factor because of the weakened immunity associated with advanced age[2]. Interestingly, within a population of liver-transplant and immunosuppressed patients in Italy, some patients tested positive for COVID-19 but none developed pulmonary disease[5]. Mortality and morbidity data from previous coronavirus outbreaks showed no fatalities in immunosuppressed groups (including transplant recipients and patients receiving chemotherapy)[3]. In more recent anecdotal reports, transplant recipients infected with SARS-CoV2 are facing variabilities in severity of disease course and outcome[7,8].

There is much speculation that the host inflammatory response (related to macrophage hyper-activation) is responsible for the severe lung and systemic complications of SARS-CoV2 and other viruses in the coronavirus family[3,5]. Patients with severe COVID-19 have been shown to have increased serum levels of pro-inflammatory cytokines including interleukin (IL)-2, IL-7, IL-6, IL-10, tumor necrosis factor (TNF)-alpha, among others[2,5]. For patients who are chronically immunosuppressed, some authors express concern that discontinuation of immunosuppression may result in an excessive increase in systemic inflammation that could actually increase susceptibility and risk of severe disease[5].

Anti-rheumatic drugs are being explored and even employed in the treatment of severe COVID-19 cases, including TNF-alpha inhibitors, anti-IL6 and anti-IL-1 biologics and Janus kinase (JAK) inhibitors[5,9,10]. The role of corticosteroids remains controversial, but it has been suggested that their anti-inflammatory effects could reduce alveolar exudation and systemic symptoms[8]. If anti-inflammatory and immunosuppressant medications do in fact have a role in treating the pulmonary complications of COVID-19, the dose must be carefully titrated to allow for sufficient host anti-viral immunity[8].

Current data and guidelines

There are no data defining the impact of initiating, continuing, or discontinuing specific immunomodulatory and immunosuppressive therapies in the context of the COVID-19 outbreak[6,11]. There are no data on risk and severity of disease in psoriasis patients on systemic therapy who are infected with the virus[6,12]. The National Psoriasis Foundation (NPF) warns that patients with severe psoriatic disease and those on potentially immunosuppressive therapies may be at increased risk of infection[13]. The American Academy of Dermatology (AAD), International Psoriasis Council (IPC), International League of Dermatological Societies (ILDS) and NPF recommend that patients who are infected with COVID-19 should discontinue immunosuppressant and biologic therapy, while there is insufficient evidence to recommendation cessation of biologics in patients who have not tested positive for COVID-19 or exhibited its symptoms[6,12-14]. These recommendations are in concordance with established guidelines for the treatment of psoriasis, indicating that biologic therapy should be stopped in the context of active infection[15]. The ACR recommends that physicians apply their current practice of managing immunosuppressive/immunomodulatory agents during episodes of infection to the circumstances about COVID-19[16]. The AAD additionally recommends that patients who have COVID-19 specific risk factors should not initiate biologic therapy at this time[6].

Systemic therapies for Psoriasis

Drugs approved by the United States Food and Drug Administration (FDA) for psoriasis and their infection warnings are summarized in Table 1**.** Currently, there are no data elucidating the risks and benefits of specific immunosuppressive and immunomodulatory therapies on the natural history of COVID-19.

Oral systemic therapies

Methotrexate

Methotrexate (MTX) is an anti-metabolite that has direct immunosuppressive effects[1,17].

MTX toxicity can result in severe infections and bone marrow suppression presenting as leukopenia[18], which has been observed in patients with

Table 1. FDA-approved systemic therapies for psoriasis and infection warnings

Systemic medication approved by FDA for treatment of psoriasis	FDA black box warning for infection
Non-biological systemic therapy	
Methotrexate	Yes
Cyclosporine	Yes
Apremilast	No
Acitretin	No
Biological Systemic therapy	
Etanercept	Yes
Infliximab	Yes
Adalimumab	Yes
Certolizumab	Yes
Ustekinumab	No
Secukinumab	No
Ixekizumab	No
Brodalumab	No
Guselkumab	No
Tildrakizumab	No
Risankizumab	No

FDA: Food and Drug Administration

COVID-19[2]. Although there is conflicting evidence, MTX toxicity is thought to cause pulmonary fibrosis[19,20], which would significantly exacerbate pulmonary deficits in the context of COVID-19 pneumonia. MTX carries a boxed warning regarding potentially fatal opportunistic infections as well as MTX-induced lung disease.

Cyclosporine

Cyclosporine exhibits potent immunosuppressive effects through its interference with pro-inflammatory signaling and its ability to suppress T-cell activation[17,21]. Patients on cyclosporine treatment are at risk for severe infections, including viral infections[17]. However, recent studies have demonstrated promising anti-influenza properties of cyclosporine A[21]. There are no studies evaluating the specific effects of cyclosporine A on the infectivity and replication of SARS-CoV2.

Acitretin

Acitretin is a vitamin A derivative that modulates epidermal differentiation and proliferation but also has immunomodulatory and anti-inflammatory properties[17]. It is not immunosuppressive, unlike other systemic agents for psoriasis and is not associated with an increased risk for infection[17].

Apremilast

Apremilast is an inhibitor of phosphodiesterase 4. It is generally accepted to have a good safety and tolerability profile, with no recommendations for routine bloodwork or monitoring[1]. Pivotal randomized controlled trials demonstrated increased rates of upper respiratory infections, nausea and diarrhea in the apremilast group compared to placebo[22]. The adverse effect of diarrhea raises concern for masking a true manifestation of COVID-19; diarrhea is a less common symptom of COVID-19 and may actually be one of the sentinel manifestations[23]. Additionally, apremilast has been shown an *in vitro* capacity to decrease the production of various pro-inflammatory cytokines, including TNF-alpha[22], which may be relevant to the pro-inflammatory cytokine storm that contributes to the severe systemic sequalae of COVID-19.

Biologics

The biologics used to treat psoriasis are classified by their interference with specific cytokine-signaling pathways: targeting TNF-alpha, IL-12/23 or only IL-23, and IL-17.

Lebwohl et al[24] summarize the rates of upper respiratory infection and overall infection for patients treated with the various biologic agents as determined by randomized controlled trials. In general, many of these agents were shown to have a slightly increased rates of upper respiratory and/or overall infection, though still comparable to placebo. TNF-alpha inhibitors are considered more immunosuppressive and carry a 'black box' warning for infection. Fatalities have been documented in patients on TNF-alpha inhibitors who were infected with influenza[4]. IL-12 is known to be involved in anti-viral immunity[24], and other cytokines including IL-17 and TNF-alpha may be implicated as well[11]. The package inserts for all biologics caution that there may be an increased risk of infection or that serious infections have occurred. However, there is no data specifically assessing the risk of infection with a coronavirus. Patients whose psoriatic disease has been well-managed on a biologic medication risk loss of efficacy with treatment cessation and subsequent re-initiation, due to possible production of anti-drug antibodies[24]. The IL-23/IL-17 axis may actually play a role in ameliorating interstitial pneumonia[25], which is a dreaded complication of COVID-19[2]. Hypotheses that controlling the "cytokine storm" portends a better outcome in patients with COVID-19 may indicate a future role for biologics in treatment of the infection.

Conclusions

Traditional immunosuppressive therapies for psoriasis including methotrexate and cyclosporine provoke significant concern for the suppression of anti-viral immunity. The use of targeted biologics is more controversial as preliminary evidence suggests a potential role for some of these therapies in preventing detrimental complications of SARS-CoV2 infection. While some forms of immunosuppression/immunomodulation may prove beneficial in COVID-19, we are limited by the lack of high-quality evidence. However, there is concern that many of these therapies confer an increased risk of infection in general. Any individual, of any age and with or without underlying comorbidities, may suffer severe complications of COVID-19[6]. Therefore, until definitive data have been accumulated addressing the exact implications of each therapy on the natural history of COVID-19, we recommend that patients on immunomodulatory and immunosuppressive therapies for psoriasis stop their treatment immediately if they are diagnosed with COVID-19 or are exposed to someone diagnosed with COVID-19, and promptly consult a dermatologist. Meanwhile, until the current situation gets resolved, we recommend that the decision to continue or to stop immunomodulatory/immunosuppressive treatment for psoriasis (MTX, cyclosporine, and all biologics) should be made on individual basis, taking into account the patient's current progress on the treatment as well as the patient's concomitant risk factors for COVID-19 as outlined by the Centers for Disease Control and Prevention (CDC).

Topical treatments have limited systemic absorption and should be used to manage psoriatic disease. Acitretin and apremilast are oral systemic therapies that may be continued or initiated during the COVID-19 outbreak without concern for affecting anti-viral immunity. Patients should be encouraged to use phototherapy, as it is a highly effective treatment for psoriasis[17], and ultraviolet radiation may actually inactivate coronaviruses[26]. Use of home phototherapy units is preferred as office visits for phototherapy sessions increase risk of exposure to SARS-CoV2.

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