Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Impact of the COVID-19 pandemic on the course and management of chronic inflammatory immune-mediated skin diseases: What's the evidence?

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Abstract Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, medical professionals have been overwhelmed by questions beyond the infection itself. In dermatology practice, clinicians have been facing difficulties about the management of chronic immune-mediated skin diseases. Issues arose, such as the grade of immunosuppression or immunomodulation, discontinuation or modification of treatment, and initiation of new treatments. In this comprehensive review, we present the current evidence about the course and management of chronic inflammatory dermatoses during the COVID-19 pandemic, focusing on psoriasis, atopic dermatitis, and hidradenitis suppurativa.

Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, medical professionals have been overwhelmed by questions beyond the infection itself. In dermatology practice, clinicians have been facing difficulties regarding the management of chronic immune-mediated skin diseases. Issues arose, such as the grade of immunosuppression or immunomodulation, discontinuation or modification of treatment, and initiation of new treatments. Literature was initially limited to correspondence and has now been enriched with data from national registries on several skin diseases.

At the very beginning of the pandemic, little was known regarding whether biologic therapies rendered patients more susceptible to the coronavirus. It was difficult to extrapolate accurate conclusions from the pivotal placebo-controlled studies. There was, however, the knowledge that in the pre-coronavirus era, respiratory infection rates were comparable to those with placebo for almost all categories of biologic agents.[1]

In this comprehensive review, we present the current evidence about the course and management of chronic inflammatory dermatoses during the COVID-19 pandemic, focusing on psoriasis (PsO), atopic dermatitis (AD) and hidradenitis suppurativa (HS).

Methods

We performed an English literature search on PubMed, using the keywords COVID-19 pandemic AND psoriasis OR atopic dermatitis OR hidradenitis suppurativa. We included all correspondence items, as well as case reports, case series, and reported data from registries and reviews. We also collected information to answer these questions:

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1. Were patients under biologic treatment more susceptible to COVID-19 infection?
2. What was the course of their skin disease during the pandemic?
3. What medical advice should clinicians provide to keep their patients in control of their skin disease and in good health during the pandemic?

Results

Psoriasis

Treatment with biologics and COVID-19 infection

Lombardy, which includes Milan, has been the Italian region with the greatest number of confirmed, hospitalized, and dead COVID-19 patients. In a study from this region, 1193 PsO patients treated with biologics and small molecules were enrolled; 17 PsO patients were confirmed with COVID-19 infection and were quarantined at home, 5 were hospitalized, and no PsO patients were admitted to intensive care unit or died. No increased risk of intensive care unit admission or death was found. From a therapeutic point of view, 262 PsO patients (22%) were taking tumor necrosis factor α inhibitors, 238 (19.9%) interleukin (IL) 12/23 inhibitors, 542 (45.4%) IL-17 inhibitors, 62 (5.2%) IL-23 inhibitors, and 89 (7.5%) small molecules.[2]

In a retrospective observational study from Verona, Italy, which is the capital of the Veneto province, during the period from February 20, 2020 to April 10, 2020, among 980 patients with chronic plaque psoriasis on biologics, there were no cases of hospitalization or death. Despite the fact that patients with psoriasis are heavily burdened by metabolic and cardiovascular comorbidities, there were no signs of an increased hospitalization or death.[3]

In accordance with the previous findings, in another study with a large number of patients who were residents in the Italian cities most at risk for the infection (Verona, Padua, Vicenza, Modena, Turin, Milan), among 5206 patients hospitalized for COVID-related interstitial pneumonia, there were only four patients with psoriasis receiving biologic treatment (guselkumab, adalimumab, ustekinumab, secukinumab). The incidence rate (IR) was 5.6 compared with an IR of 5.9 in the general population.[4]

In a study from Naples, the capital of Catania, Italy, based on telephone consultations, from March 9, 2020 to April 8, 2020, among 168 patients with psoriasis (75 on anti-IL-17 treatment [golimumab], 41 on ustekinumab treatment, and 14 on anti-IL-23 drugs guselkumab or risankizumab), no patient had confirmed COVID-19 using nasal or pharyngeal swab examination.[5]

A national, multicenter, cross-sectional study during consultations or teleconsultations, including adult psoriasis patients receiving systemic treatment for psoriasis (classic systemic treatment and/or biologics) was conducted in France from April 27, 2020 to May 7, 2020.

Among the 1418 patients included, 12 patients had been diagnosed with COVID-19 infection and 5 (0.35%) were hospitalized. Three of the hospitalized patients had other risk factors for severe infection (obesity, Crohn disease). The authors did not report a significant difference in the number of severe cases of COVID-19, whether the patient was in the treatment initiation period (1 out of 230 patients) or in the maintenance period (4 out of 1188 patients).[6]

Hidradenitis suppurativa

Treatment with biologics and COVID-19 infection

Turin, the capital of the Piedmont region, is one of the areas with the highest number of deaths caused by COVID-19 infection in Italy. According to a retrospective observational analysis of the moderate and severe HS patients under systemic treatment (n = 96) in the Dermatology Department of the Turin University Hospital, there were no deaths from COVID-related disease or hospitalization for COVID-related interstitial pneumonia.[7] Among HS patients in whom treatment continued during the pandemic, 30.2% received systemic treatment with antibiotics, 8.3% retinoid, 47.9% adalimumab, 11.5% secukinumab, and 2.1% apremilast.[7]

Further real-world evidence from registries regarding HS course and treatment during the pandemic is anticipated.

Atopic dermatitis

Treatment with biologics and COVID-19 infection

In a series of adult patients with AD from Brescia, Lombardy, among 71 adult patients treated with dupilumab treatment for a mean duration of 7.8 months, only 2 patients (2.8%) were confirmed with COVID-19 infection. One was a man with multiple comorbidities (asthma, hypertension, severe obesity, depressive syndrome) who was hospitalized without sequelae.[8]

In Milan, among 245 patients in therapy with dupilumab, only 2 (0.82%) developed COVID-19 infection. None of them had complications.[9]

In another study from the Bergamo area in Italy, 30 patients with AD on dupilumab therapy were contacted by telephone or made a dermatologic visit to the hospital. None of the patients reported a COVID-19 infection confirmed by nasal swab or serologic testing.[10]

In a multicenter retrospective study from two tertiary academic hospitals in Toronto, Canada, of the 162 patients on dupilumab, only 1 (0.62%) had temporarily discontinued treatment due to patient-driven concerns and none due to infection.[11]

Discussion

During the first weeks of the pandemic, especially due to the unpredictable course of COVID-19 infection, there was a debate on what to advise patients. Middle-aged or older

men with psoriasis and comorbidities, such as diabetes mellitus or cardiovascular diseases, are more susceptible to severe COVID-19 infection. Traditional immunosuppressive drugs, including methotrexate and cyclosporine, affect the entire immune system and have an impact on the host defense against viral infections. Given the fact that the immunomodulating actions of conventional systemic agents are dose related, it has been suggested to lower the doses during the pandemic COVID-19 infection; that is, cyclosporine $\leq$1 mg/kg per day and methotrexate $\leq$10 mg/week. Low-dose acitretin may be a well-tolerated alternative because there is no evidence of COVID-19–related harm (or that of any RNA virus) from systemic retinoids.[12,13]

Treatment with biologic agents is targeted and may even protect against COVID-19 pneumonia, reducing the overall inflammation.[14] In patients with severe COVID-19, especially during the acute respiratory distress syndrome, large amounts of proinflammatory cytokines are released, including some that may be overexpressed in psoriasis, such tumor necrosis factor α and IL-23. An exaggerated immune response has been hypothesized to cause the widespread lung damage associated with SARS-CoV-2.[15,16] It has been also hypothesized that treatment for patients with symptomatic COVID-19 would benefit from additional therapy that lessens this inflammatory response, rather than being based solely on therapies that control virus replication.[17] These observations have led to the hypothesis that anti–tumor necrosis factor or anti–IL-23/IL-17 axis blockade may even have a possible beneficial role on immune regulation in COVID-19 infection and in acute respiratory distress–related mortality.[15-17]

Adalimumab is currently being evaluated for use in treating severe COVID-19 pneumonia.[12] Case reports of patients receiving anti–IL-23/IL-17 axis inhibition having favorable outcomes of their COVID-19 infection also support this hypothesis.[18,19]

The positive role of biologic therapy on respiratory function has been shown in psoriatic patients who display baseline airway inflammation that clears after antipsoriatic therapy.[2] This provides a rationale to continue biologics in PsO patients to prevent the lung-skin inflammatory axis and inhibit progression to the hyperinflammatory phase.[2]

The existing evidence indicates that the most important risk factors leading to severe illness for COVID-19 patients are such comorbidities as hypertension, diabetes, and obesity, suggesting a concern for fragile or elderly patients, rather than discontinuing treatment in all patients. In vulnerable patients it is better to suspend treatment in case of flu-like findings, COVID-19 specific anosmia or ageusia, or exposure to high-risk contact with infected people.[20] There is already a negative impact on the course of psoriasis and on the quality of life due to the psychological consequences of forced quarantine. A preventive discontinuation of an effective treatment and the already impaired physiologic and emotional state may potentially worsen psoriasis, and thus this "preventive choice" is considered as rather poor.[5]

In the absence of hard data, if the patient has a clinically active COVID-19 infection with fever, cough, dyspnea, or a positive reverse transcription–polymerase chain reaction test, initiation of immunosuppressive treatment should be postponed until resolution of the infection.[21] Additionally, testing for SARS-CoV-2 immunoglobulin G may identify patients who have gained some immunity against COVID-19 and in whom initiation of systemic treatment may be safe.[21]

Psoriasis is a complex disease and thus, when no signs of infection are present, it is considered rather harmful to interfere with its balance without an established indication.[22] Additionally, discontinuation of biologic treatment may lead to increased health care costs due to the unavoidable disease relapse, the subsequent reintroduction of biologic therapy with likely lower efficacy in the same patient after interruption, and the need to switch to another agent.[23] According to the initial data from French centers, there is no increased incidence of severe COVID-19 infection in psoriasis patients who are receiving biologics in the treatment initiation period compared with those in the maintenance period.[6]

Hidradenitis suppurativa is managed effectively with biologic agents, especially when there is a high disease burden. Based on the published data from adalimumab clinical trials, there is a minimal difference in the risk of upper respiratory tract infections in HS patients on adalimumab versus placebo.[24] The existing evidence shows that HS patients under adalimumab treatment have not been more susceptible to COVID-19 infection.[7]

In AD treatment, dupilumab inhibition of IL-4 and IL-13 does not seem to increase the risk of infection by COVID-19 or worsen its clinical course in patients, even in those with severe AD.[8,9] Janus kinase inhibition with baricitinib has been studied in the treatment of AD. There are also data about its possible use in COVID-19 infection.[25] AP2-associated protein kinase 1 is a known regulator of endocytosis, and its disruption may interrupt the passage of the virus into cells and the intracellular assembly of virus particles. Baricitinib is able to inhibit Janus kinase 1 functions and to bind the cyclin G–associated kinase, another regulator of endocytosis of virus.[25] Based on these preclinical data, treatment with either baricitinib or upadacitinib should be continued during the pandemic.[25]

Conclusions

Observational data on COVID-19 outcomes in psoriasis, hidradenitis suppurativa, and atopic dermatitis on a global scale are needed. PsoPROTECT (www.psoprotect.org) and SECURE-AD (www.covidderm.org) are two web-based registries for clinicians to report COVID-19 outcomes in psoriasis and atopic dermatitis, respectively.[26]

When more knowledge about COVID-19 infection becomes available, more data related to patients with immune-mediated skin diseases under biologic therapy who have contracted the infection will facilitate better quantification of the

risks and benefits of biologic therapy and better define a personalized approach based on comorbidities.

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