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Current Knowledge on Psoriasis During the Covid-19 Pandemic

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ABSTRACT Psoriasis is a chronic inflammatory disease associated with a defective epidermal barrier, in which the immune system is already activated in lesional sites of the skin, and it is thus possible that affected individuals can have different immunologic rates of viral response. This is especially important in the era of the novel coronavirus disease (COVID-19) that is affecting the entire world. Patients with psoriasis are often receiving systemic therapy which includes immunosuppressive and biologic therapy, so this new infectious disease has raised concerns among dermatologists regarding psoriasis treatment. Some of the risk factors of psoriasis are obesity, diabetes mellitus, and hypertension – all of which are diseases linked with negative outcomes and higher severity of COVID-19. Psoriasis is mediated by inflammatory cells and proinflammatory cytokines such as IL-17, IL-23, IFN-γ, and TNF-α, and patients with skin diseases have been shown to be more susceptible to COVID-19 infection, but with a less severe disease course. As an anti-inflammatory agent, vitamin D could play a significant role in the future as a possible treatment for reducing the risk and severity of psoriasis and COVID-19. It has been suggested that patients treated with biologic therapy should continue treatment, as it has not been shown to cause severe complications of the COVID-19 disease. Preventive measures, including vaccination, should be taken to minimize the risk of infection and severity of the clinical outcome.

KEY WORDS: psoriasis, COVID-19, treatment, biologic therapy, vaccination

INTRODUCTION

Psoriasis is an immune-mediated, chronic skin disease causing red, itchy, and crusty patches that affects approximately 125 million people globally (1). There are different clinical types of psoriasis, and the most common type being plaque psoriasis (psoriasis vulgaris) that is found in about 80% of people with psoriasis. Other types mentioned in this review include guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. Pustular psoriasis is a rare condition found in between 1.1% and 12.0% of all cases of psoriasis (2). Management of psoriasis includes the use of topical and systemic agents, depending on the disease severity (3). One of the most common comorbidities associated with psoriasis is psoriatic arthritis. It is a form of arthritis that develops in up to 30% of patients diagnosed with psoriasis (4).

Since December 2019, the COVID-19 pandemic has been a challenge for the whole world, and especially for healthcare workers. The coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms of COVID-19 infection vary from person to person, but the most common are dry cough, fatigue, high body

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temperature, loss of smell, and body ache. While the majority of people present as asymptomatic or with mild symptoms, some may experience more severe symptoms such as shortness of breath or difficulty breathing (5).

How the COVID-19 pandemic has affected patients with this chronic skin disease, and especially its impact on the treatment of psoriasis, is the focus of this review.

WHAT DO THE IMMUNOPATHOGENESIS OF PSORIASIS AND COVID-19 INFECTION HAVE IN COMMON?

Psoriasis is characterized by multiple interactions between various immune cells, where T-cells have a major role. There are three types of dendritic cells (DCs) that have a role in the initial part of the disease (Langerhans cells, dermal DCs, and plasmacytoid DCs). When the trigger occurs, antigen-presenting cells (APCs) become activated and produce proinflammatory cytokines. Plasmacytoid dendritic cells (PDCs) produce IFN-α, while Langerhans cells produce IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) (6,7). This process leads to interaction with naive T-cells. Production of IL-6, TGF-β, and IL-23 by DCs is necessary to stimulate differentiation of T-cells into Th17 helper cells. Migration of Th17 helper cells into the skin causes secretion of IL-17, which activates keratinocytes (8). Activated keratinocytes secrete more cytokines, resulting in the recruitment of more immune cells (9).

Some proinflammatory cytokines produced in COVID-19 infection include IL-2, IL-10, IL-12, IL-17, and TNF-α, many of which are also important in the immunopathogenesis of psoriasis (10). Moreover, results from a study by Han et al. showed that serum from patients with COVID-19 contained high levels of cytokines such as TNF-α, IL-2, IL-4, IL-6, IFN-γ, and IL-10 (11).

IS IT POSSIBLE FOR SARS-CoV-2 TO ACT AS A TRIGGER FOR THE ONSET OR EXACERBATION OF PSORIASIS?

Psoriasis is a complex, multifactorial disease that is a result of both extrinsic and intrinsic factors. Extrinsic risk factors include mechanical stress, air pollution, drugs, vaccination, infection, smoking, and alcohol, while intrinsic factors include obesity, diabetes mellitus, hypertension, and mental stress (12). It is known that various infections can act as a trigger for psoriasis. The most well-described association is between Streptococcal infection and guttate psoriasis (13). Additionally, studies have described a connection between the development of psoriasis and infection with Staphylococcus aureus and human immunodeficiency virus (HIV) (12).

Mathieu *et al.* described the first case in the literature of the new onset of psoriasis in a patient with COVID-19 infection. This case report described a 62-year-old woman with comorbidities including diabetes, obesity, and hypertension who developed psoriasis two weeks after SARS-CoV-2 infection. She presented with palmoplantar pustules, palmar erythema with hyperkeratosis, papulopustular skin lesions on the extremities, and plaques on the trunk and scalp. Skin biopsies confirmed the diagnosis of pustular psoriasis. Furthermore, this patient had a positive family history for psoriasis, namely an aunt and a cousin with psoriasis (14).

In Italy, doctors from the Humanitas Clinical and Research Center in Milan diagnosed the first case of psoriatic arthritis triggered by SARS-CoV-2 infection in the case of a 27-year-old woman. She had a history of irritable bowel disease and a positive family history of psoriasis (15).

Except for triggering new onset of psoriasis and psoriatic arthritis, several cases showed that SARS-CoV-2 can also exacerbate psoriasis. Shakoei et al. described the case of a 47-year-old woman that had been diagnosed with pustular psoriasis 4 years ago. In that period, she used methotrexate for 1 year and was without lesions during that time. However, new lesions developed 3 weeks after COVID-19, indicating exacerbation. She presented with pustular lesions on the trunk and extremities (16).

Another case report described the exacerbation of psoriasis after hydroxychloroquine and oseltamivir therapy in a 71-year-old woman with a COVID-19 infection. The patient developed silver-scaled psoriatic plaques on the fourth day of treatment. The patient had a history of psoriasis that had occasionally activated since childhood (17).

THE ROLE OF VITAMIN D IN PSORIASIS AND COVID-19

Vitamin D is a prohormone with a few active metabolites that act as steroid hormones. Vitamin D is best known for its regulation of calcium and phosphate metabolism, but it also has a role in immunomodulation (18). The CYP27B1 gene, which encodes an enzyme that converts vitamin D to its active form, is also expressed in keratinocytes and activated macrophages, leading to an active form of vitamin D and performance of its functions (19). One of those functions is enhancing macrophage antimicrobial activity and stimulating the production of cathelicidin

LL-37, which has antibacterial, antifungal, and antiviral effects. Moreover, vitamin D induces autophagy in macrophages which also helps the immune system defend from opportunistic infections (20). It has been shown to have antiviral effects against respiratory viruses by affecting the viral envelope and host target cell (19). Expression of CYP27B1 is found in bronchial epithelial cells as well and is induced by inflammation, which indicates the role of vitamin D in the host defense mechanism (21). Moreover, vitamin D suppresses the production of proinflammatory cytokines such as IL-2, IL-6, and IL-17 and increases the production of IL-10, an anti-inflammatory cytokine (19). Another intriguing fact is that the SARS-CoV-2 spike protein binds to the human angiotensin-converting enzyme 2 (ACE 2) receptor, which is expressed in the lungs, heart, endothelium, intestine, and kidneys (22). A recent study has shown that ACE 2 is an interferon-stimulated gene (23) which causes the disease COVID-19. Increased expression of IFN-γ has been reported in psoriatic lesions, and it is possible that this increases the expression of ACE 2, which may lead to COVID-19 skin manifestations and worsening of the psoriatic condition (24). Vitamin D acts as a modulator of the renin-angiotensin pathway and decreases the expression of ACE 2, and it has therefore been proposed that vitamin D supplementation could decrease the risk and severity of COVID-19 infection (19).

Although vitamin D has a beneficial effect on overall human health, how it should be administered is still controversial, and what dose and what level of serum is optimal. The data about clinical efficacy in psoriasis and COVID-19 are not conclusive, and more studies should be done in the future to define the specific dose of vitamin D supplementation and its *in vivo* effects.

OBESITY IN PSORIASIS AND COVID-19

Obesity is a risk factor for numerous diseases such as diabetes type 2, hypertension, and kidney and heart disease, all of which important comorbidities of psoriasis, but obesity also induces a proinflammatory state that can lead to greater susceptibility to contracting an infection. Moreover, obesity is an independent risk factor for psoriasis. Psoriasis-associated systemic inflammation promotes the inflammation of adipose tissue, leading to adipokines releasing and further stimulating systemic inflammation (25). Another study that compared obese and nonobese patients with chronic obstructive pulmonary disease (COPD), found increased expression of ACE 2 in the bronchial epithelium in obese patients, making them more susceptible to COVID-19 (26). Higher BMI is related to severe disease. Severe acute respiratory syndrome coronavirus 2 utilizes angiotensin converting enzyme 2 (ACE2). Epicardial adipose tissue inflammation is believed to cause cardiovascular disorders that are most prevalent in patients with psoriasis. Both COVID-19 and psoriasis can cause pericardial inflammation in obese patients and can lead to endothelial vascular damage, but their mutual interaction should be studied further (25).

TREATMENT OF PSORIASIS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has raised concerns among dermatologists regarding psoriasis and its treatment. Since patients with psoriasis are more prone to thrombosis and other comorbidities, which include known risk factors for SARS-CoV-2 infection, such as obesity and cardiovascular diseases, therapy decisions must be made carefully. The treatment for psoriasis is normally based on disease severity. For limited cutaneous disease, topical treatment – corticosteroids in combination with vitamin D analogues or other agents or targeted phototherapy – can be the only treatment option. On the other hand, oral systemic medications and full-body phototherapy are required for extensive disease. Acitretin, apremilast, methotrexate, cyclosporine, and biologics as treatment regimens should be chosen based on the patient's comorbidities, preferences, and treatment response. Patients with autoimmune diseases, such as psoriatic disease, have been found to have a higher risk of COVID-19 than controls (odds ratio [OR], 2.19; 95% confidence interval [CI], 1.05-4.58) in a meta-analysis of 7 case-control studies, primarily atributed to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) use (27). However, patients with psoriasis have similar rates of infection with SARS-CoV-2 and COVID-19 outcomes as the general population (28). A cytokine storm, meaning a release of a large number of proinflammatory cytokines (IFN-α, IFN-γ, IL-1-β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-β) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10) may occur in COVID-19 and cause acute respiratory distress syndrome (ARDS), which is the main cause of death (29,30). Therefore, immunosuppressive therapy could be associated with a lower risk of severe COVID-19.

Furin and ACE-2 mRNA levels in blood cells can be used as a predictor for COVID-19 severity. In patients with untreated psoriasis, furin is significantly overexpressed and may be the reason for the higher risk of infection and more severe disease course in these patients (31). Considering a potential risk of elevated furin levels in correlation with COVID-19 severity,

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a successful treatment could lead to lowering that risk.

Acitretin and apremilast as non-immunosuppressive agents

Acitretin is a systemic, second-generation retinoid that affects JAK-STAT signaling pathway inhibiting keratinocyte proliferation (32). Retinoids inhibit cell proliferation and keratinocyte differentiation. Acitretin reduces Th1 and Th17 cell activity and the expression of IFN-γ (33). Acitretin is not an immunosuppressant agent and is more effective in treating pustular psoriasis compared to methotrexate, cyclosporine, and PUVA therapy (34). Palmoplantar and erythrodermic psoriasis can also be treated effectively with acitretin.

Acitretin is beneficial for its immune-sparing mechanism of action. In the present COVID-19 pandemic, acitretin appears to be a safe option since it has no immunosuppressive effects (35). Another immunomodulatory agent that should be considered in the treatment of psoriasis in the coronavirus pandemic is apremilast. Apremilast does not affect B- or T-cells and immunoglobulin secretion (36). Apremilast has been shown not to increase the risk of severe COVID-19 in patients with psoriasis (37). Because of its specific mechanism of action, apremilast is not connected with the cytokine storm or COVID-19 infections and is considered a safe option (38).

Methotrexate and cyclosporine

Nonbiologic medications, including the immunosuppressants methotrexate and cyclosporine, are typically easier to stop and restart due to a shorter half-life. These medications likely have a concerning level of risk and should be discontinued when viral symptoms are present (39).

Methotrexate has anti-inflammatory, antiproliferative, and immunosuppressive properties through the inhibition of dihydrofolate reductase and consequently synthesis of DNA. Cyclosporine A (CsA) is an immunosuppressive drug that binds to cellular cyclophilins to inhibit calcineurin. CsA can inhibit the replication of some RNA viruses and might be a good candidate against COVID-19 (40). However, in general both methotrexate and cyclosporine are associated with an increased risk of infection. Furthermore, one of the main adverse effects of cyclosporine is hypertension, which makes patients more prone to developing severe COVID-19 infection (41).

Biologic therapy

There are currently 11 biological therapies approved for psoriasis (42). The mechanisms of their immunosuppressive effects consist in targeting some of the mediators of inflammation, such as TNF-α, IL-17, and IL-23. When the COVID-19pandemic started, there was concern that treatment with the above-mentioned therapies may reduce resistance to infection. The safety profile of biologic agents is better than that of conventional immunosuppressive therapies, but there is a concern that using these agents might increase the risk of viral infections (43).

What we know today is that stopping biological medications may lead to psoriasis flares and erythroderma, which may require hospitalization (42). There is also a possibility of reduced response to re-treatment, most commonly due to immunogenicity (44). One more reason against the discontinuation of biologic therapy is the possibility of inducing higher proinflammatory states and therefore worsening the cytokine storm (45).

In a large, global case series, patients with psoriasis and risk factors such as male sex, older age, and nonwhite ethnicity were associated with a greater risk of hospitalization for COVID-19. Furthermore, cardiovascular disease, hypertension, and chronic liver disease were more prevalent in hospitalized patients. COVID-19 hospitalization was less frequent in patients receiving biologics compared with the patients using nonbiologics (46). Lower rates of mechanical ventilation and death were found in patients receiving biologic therapy than in those receiving nonbiologic systemic therapy or no systemic therapy at all (46).

In a retrospective multicenter cohort study, no significant difference was found in the rates of hospitalization in patients treated with biologic therapy compared with the general population when stratifying by age – under and above 65 years or by class of biologic (28). The reason for this may be because systemic biologic treatment can significantly reduce expression of furin, normalizing levels after 3 and 12 to 24 months (31). A further hypothesis is that biologic therapy prevents cytokine storms and therefore has a beneficial effect on the course of COVID-19. Moreover, tumor necrosis factor inhibitors decrease TNF-α-converting enzyme-dependent shedding of the ACE2 ectodomain crucial for SARS-CoV-2 cell penetration (47).

There is also a hypothesis that receptors for TNF-α are promoters of the pathogenesis of SARS-CoV-2. On the other hand, treatment with TNF-α inhibitors showed an increase in overall infections and upper respiratory infections of up to 7% compared with the placebo group, except for etanercept, which showed no increase (43). In summary, the use of biologics is associated with a reduced risk of hospitalization

compared with nonbiologic systemic therapy or no therapy (46). Evidence suggests that biologics used for treating psoriasis do not increase the risk of viral infections or their complications, but a personalized approach is recommended.

VACCINATION

Preventative health measures are needed that can reduce the risk of infection and severity of COVID-19 and its course. There is currently no data on the efficacy and safety of COVID-19 vaccines in patients on immunosuppressive therapy, including patients with psoriatic disease treated with conventional or biologic drugs. Since the approved vaccines do not contain the live virus, they are expected to be safe in patients on immunosuppressants (48).

Because of the immunosuppressive therapy and its mechanism of action, the immune response against the COVID-19 vaccine may be impaired. When deciding on vaccination, the question is whether to temporarily postpone taking the immunosuppressive therapy. In doing so, the consequences arising from the discontinuation of the therapy should be taken into account, which may result in an increase in disease activity, ie. relapse or loss of response to therapy.

What we know now is that, secukinumab, an IL-17A inhibitor, does not affect the humoral response to influenza vaccine in patients with psoriatic arthritis (49). On the other hand, immune response on pneumococcal vaccination was reduced in patients with rheumatoid arthritis on methotrexate (50). Considering all the facts, COVID-19 vaccination should be recommended to patients with psoriasis, even though we have no evidence of the degree of protection it provides.

CONCLUSION

In these times when the COVID-19 pandemic is taking its toll on human health across the world, it is important not to neglect other diseases and conditions. Patients with psoriasis who are treated with systemic medications that affect their immune response should be in the priority group for dermatologists, especially elderly patients with coexisting morbidities such as diabetes, hypertension, and obesity. Studies have shown that biological therapy can be continued during the pandemic and that it does not influence the development of severe complications of COVID-19 disease. According to current studies, skin conditions are associated with an increased risk of COVID-19 but are also associated with a less severe disease course. Although the efficacy of systemic vitamin D intake for psoriasis and COVID-19 treatment has not been demonstrated, its anti-inflammatory activity should be taken into account, and more studies on this subject are needed in the future. Preventative health measures such as vaccination that reduce the risk of COVID-19 infection are recommended.

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