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REVIEW ARTICLE

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Psoriasis and COVID-19: A narrative review with treatment considerations

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Abstract

Coronavirus disease (COVID-19) is a highly contagious respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 outbreak has been declared a pandemic by the World Health Organization on March 2020. The pandemic has affected the management of psoriasis not only for those who are under treatment but also for those who are about to begin a new therapy to control their disease. An increasing number of studies in the current literature have focused on the relationship between psoriasis and COVID-19 from different perspectives. This narrative review includes searching the PubMed and Web of Science databases using the keywords "psoriasis," "psoriatic arthritis," "coronavirus," "COVID-19," and "SARS-CoV-2." The search was supplemented by manual searching of reference lists of included articles. A total of 11 relevant original investigations and 6 case studies was identified. The search was updated in May 2019. Due to the absence of randomized controlled trials, it is not likely to have a robust evidence-based approach to psoriasis management in the era of COVID-19. However, the current literature may provide some clues for safety considerations. Conventional immunosuppressive therapies such as methotrexate and cyclosporine, and anti-tumor necrosis factor agents should not be preferred due to increased risk of infection, especially in high-risk areas. The use of cyclosporine may pose additional risk due to the side effect of hypertension, which has been reported to be associated with susceptibility to severe COVID-19. Considering that the current literature has provided no conclusive evidence that biologics increase the risk of COVID-19, withdrawal of these agents should be reserved for patients with COVID-19 symptoms. The treatment approach should be personalized, considering the advantages and disadvantages for each case separately.

KEYWORDS

coronavirus, COVID-19, pandemic, psoriasis, psoriatic arthritis

1 | INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease associated with significant morbidity extending beyond the cutaneous manifestations.[1] The disease affects about 2% to 3% of the population worldwide, and its management requires qualified professionals to provide high-quality care.[2,3] Coronavirus disease (COVID-19) is a highly contagious respiratory infection caused by severe acute

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respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 outbreak, which caused thousands of deaths, has been declared a pandemic by the World Health Organization on March 2020.[4] The pandemic has been reported to modify the course of many diseases, and psoriasis is not exempt from the impact of the outbreak.[5,6]

2 | METHODS

This narrative review includes searching the PubMed and Web of Science databases using the keywords "psoriasis," "psoriatic arthritis," "coronavirus," "COVID-19," and "SARS-Cov-2." The search was supplemented by manual searching of reference lists of included articles. A total of 11 relevant original articles and 6 case studies was identified. The search was updated in May 2019.

2.1 | The impact of pandemic on the course of psoriasis

The COVID-19 pandemic has altered the approach to all patients necessitating close contact during a visit, including dermatologic consultations. The healthcare system was overwhelmed in many countries, and many centers could not cope with the vast number of patients. Patients with psoriasis were not exempt from this situation and had only limited access to required healthcare settings in many countries. Many centers were able to maintain scheduled treatments for only selected patients.[3] Limited availability of dermatology care services caused exacerbation of preexisting cases of psoriasis, while new cases failed to be diagnosed. "Stay at home" orders issued by many authorities to limit the spread of the infection were another reason for fewer patients applying for outpatient services.[7]

Emotional stress is another factor that may act as a catalyst for the onset and aggravation of psoriasis.[8] Kutlu and Metin suggested that the burden of stress prompted by the COVID-19 pandemic might raise the number of psoriasis cases demanding dermatology visits.[9]

A recent web-based study investigating the association of outdoor activity restriction and income loss with patient-reported outcomes of psoriasis during the COVID-19 pandemic showed that 43.7% of 926 patients described moderate-to-much worsening of psoriasis. Outdoor activity limitation was found to be positively correlated with the worsening of psoriasis, stress, and anxiety and depression. Likewise, income loss was associated with the exacerbation of psoriasis, stress, and anxiety and depression.[10]

Maximizing the psychosocial support available to patients with psoriasis during the pandemic may play a significant role in controlling disease activity.

2.2 | The impact of COVID-19 itself on the course of psoriasis

Patients with COVID-19 may show characteristics of hyperinflammation caused by the overproduction of cytokines. Biomarkers of inflammation such as C-reactive protein and ferritin have been found significantly elevated in patients with COVID-19.[11] Given the crucial role of inflammation in the pathogenesis of psoriasis, it can be suggested that hyperinflammation status caused by COVID-19 may also alter the course of psoriasis. In their series of 52 patients, Kutlu and Metin found that 9.6% of patients with COVID-19 who were previously admitted to the dermatology outpatient clinic had psoriasis. They concluded that patients with psoriasis may be more vulnerable to COVID-19.[9] Ozaras et al reported a case of psoriasis worsened possibly due to COVID 19. The authors implied that hyperinflammation status generated by COVID-19 itself might exacerbate psoriasis.[12]

2.3 | COVID-19-related medications and psoriasis

At this time, there are no medications that have been proven to be effective for the prevention or treatment of COVID-19. However, various antiviral agents, immunotherapies, and vaccines continue to be investigated as potential therapeutics.

Hydroxychloroquine (HCQ) has been licensed since 1955 for the prevention and treatment of malaria.[13] The studies suggest that HCQ may have antiviral effects. Notwithstanding the absence of obvious evidence, Food and Drug Administration allowed emergency use of HCQ in hospitalized patients without alternative treatment options.[14] Psoriasis has been reported to be induced or aggravated by HCQ. Most recently, Kutlu and Metin reported a 71-year-old patient with COVID-19 to have an aggravation of preexisting psoriasis following HCQ and oseltamivir administration.[5] Although the precise causes of this effect are not entirely understood, it has been reported that HCQ may increase the production of interleukin (IL)-17 resulting in enhanced keratinocyte growth.[15] In their recent systematic review investigating the effects of HCQ on psoriasis, Sachdeva et al identified 18 cases of psoriasis affected by HCQ. Of the 18 cases, 50.0% had new-onset psoriasis, 27.8% experienced an aggravation of psoriatic lesions, and 22.2% showed a relapse of psoriasis after HCQ treatment. Besides well-known adverse effects of HCQ, including prolonged QT and cardiomyopathy, it is also crucial to recognize the possible impact of HCQ on worsening, recurrence, or new onset of psoriatic lesions. However, given the absence of clear evidence, more extensive studies are needed to validate the findings reported so far.[16]

Azithromycin is a macrolide antimicrobial agent with documented in vitro antiviral and anti-SARS-CoV-2 effects. It may modify SARS-CoV-2 entry by interfering between its spike protein and host ACE2 receptor. Clinical studies have revealed the ability of azithromycin to decrease the viral load. It has also been shown to improve mortality in the Middle East respiratory syndrome (MERS)-coronavirus infection.[17]

A single-blind, randomized-controlled study has shown that azithromycin may be a potential therapeutic option for chronic plaque psoriasis via its effects on superantigen-producing group A streptococcus, and by its possible immunomodulatory effect on epidermal Langerhans cells and keratinocytes.[18] In another study, Huang et al found that azithromycin inhibits TLR7 signaling in dendritic cells and improves the imiquimod-induced psoriasis-like cutaneous inflammation in mice.[19] It can be hypothesized that the use of azithromycin in

COVID-19 cases with preexisting psoriasis may alleviate psoriatic lesions. However, it is obvious that more observations and prospective studies are needed to confirm or reject this hypothesis.

2.4 | Treatment of psoriasis in the era of COVID-19

2.4.1 | Acitretin

Acitretin has anti-inflammatory properties and inhibits cell differentiation without immunosuppressive effects. In their cohort study, Dommasch et al found that patients with psoriasis on acitretin treatment showed no increased risk of viral or respiratory infection.[20] Caselli et al showed that retinoids may have antiviral effects on human herpes virus.[21] The effects of retinoids on SARS-Cov-2 remain unknown. Although acitretin has not been proven safe in patients with COVID-19, it can be preferred during the pandemic because it has no immunosuppressive effects.

2.4.2 | Methotrexate and cyclosporine

Both methotrexate and cyclosporine are associated with an increased risk of infection. The overall frequency of contracting pneumonia in patients with psoriasis using methotrexate has been reported to be 0.8%.[22] Cyclosporine only slightly increases the risk of respiratory tract infections. However, the main adverse effects of cyclosporine, such as hypertension and renal dysfunction, may pose more severe risks for patients contracted COVID-19. It should be noted that patients with hypertension are more prone to develop severe COVID-19 infection.[23] Unexpectedly, Wilde reported that cyclosporine strongly inhibits in vitro replication of MERS-coronavirus, while its in vivo effects remain unknown.[24]

Despite the impact of these immunosuppressive agents on the course of COVID-19 is clearly unknown, several dermatology societies have recommended to withdrawn or suspend immunosuppressive treatments in the case of COVID-19 diagnosis until the patient recovers from the infection. However, the decision has been left to the cooperation between the patient and physician in charge, considering the advantages/disadvantages for each case separately.[25,26]

2.4.3 | Biologics and anti-IL therapies

Biologics inhibit immune-mediated pathways including distinct cytokines. Therefore, they may pose a possible risk of enhanced sensitivity to infections. However, there is no clear evidence supporting the withdrawal of biologics for most patients with psoriasis due to the risk of infection. Some authors have not recommended the withdrawal of tumor necrosis factor alpha (TNFα) inhibitors and anti-IL biologics due to "likely moderate risk" in the case of mild viral symptoms.[27] Other authors have proposed avoidance of TNFα inhibitors for patients with cutaneous diseases in regions with high infection rates and discontinuation of all biological agents in the case of exposure to COVID-19 cases.[28] Nevertheless, whether discontinuation of immunomodulatory treatments may enhance the risk of cytokine storm is remained unknown.

Several studies reported comparable risks of infections in patients with psoriasis receiving biologic agents. In a study investigating the risk of serious infection in patients with psoriasis receiving biologics, the highest risk has been reported for infliximab. The authors found no significant increases in the risk of serious infection for etanercept, adalimumab, or ustekinumab compared with nonbiologic systemic therapies or methotrexate only.[29] Another study has shown no significant difference between the biologics and other systemic therapies in terms of the risk of serious infection.[30] In a recent study, including 515 patients with psoriasis on biologics, psoriasis worsened in 9 of the 27 (33.3%) patients who left their treatments. None of the 488 patients who survive treatment described any COVID-19-related symptoms, supporting the safety of biologic agents in patients with psoriasis.[31] In a cross-sectional, questionnaire-based study, the authors found that COVID-19 knowledge prevents biologics discontinuation. The authors concluded that dermatologists should inform their patients about COVID-19 to avoid their loss of compliance.[32] In a multicenter study, the authors reported that 23 patients with psoriasis on biologics had COVID-19 symptoms but they did not stop treatment. The authors did not observe a more severe course of suspected COVID-19 signs in patients who maintained treatment.[33] In their case series including four COVID-19 patients with psoriasis on biological drugs, the authors found that only one patient, who was on guselkumab, exhibited a severe form of COVID-19. Another patient, who was on IL-12/23 inhibitor ustekinumab, showed only mild symptoms. The other two cases did not show any symptoms. The authors concluded that biological drugs may play a protective function against the onset and the course of the infection.[34] On the other hand, Benhadeu et al reported improvement of COVID-19 symptoms following guselkumab injection in a patient with psoriasis.[35] Messina et al also reported a case of COVID-19 in a patient with psoriasis on IL-23 inhibitor guselkumab. The patient showed only mild symptoms and the authors concluded that IL-23/IL-17 pathway inhibition may not be deleterious in the setting of COVID-19 infection.[36] Balestri et al reported a patient who was infected during the induction regimen of IL-17 inhibitor ixekizumab. The patient was tested positive for SARS-CoV-2 following contact with a COVID-positive patient. The patient was completely asymptomatic, although he continued the treatment as previously scheduled.[37] Considering that the interference of IL-17/23 pathway may have beneficial outcomes in COVID-19, ixekizumab is being investigated for the treatment of COVID-19 infection.[36] In a large cohort study including 1193 patients with psoriasis on biologics and small molecules, the authors found that patients on biologics were at a greater risk to test positive for COVID-19 and to be hospitalized. However, they reported no increased risk of intensive care unit admission or death.[38] In a retrospective multicenter study including 206 patients with psoriasis on biologics, the authors found no significant number of hospitalizations or deaths from COVID-19.[39] In another retrospective study, including 980 patients with psoriasis on biologics, the authors have found no early signal of

an increased hospitalization or death from COVID-19.[40] Finally, in a telephone consultation-based study including 168 patients with psoriasis on biologics, the authors did not observe a high frequency of COVID-19 or related symptoms.[41]

The current literature has shown no conclusive evidence that biological agents increase the risk of COVID-19. Therefore, preventive withdrawal of treatment should be avoided and reserved for patients with COVID-19 symptoms. The cessation of biologics may also be considered for patients having contact with a confirmed case of COVID-19. Unnecessary biologic withdrawal may cause worsening of psoriasis, increased disease burden, unfavorable impact on the quality of life, and raised healthcare costs. Moreover, the subsequent return to biologic therapeutics can be related to switching toward more expensive drugs because of the limited efficiency of biologics in the same patient after their interruption.[42]

2.4.4 | Psoriatic arthritis and COVID-19

Psoriasis and psoriatic arthritis (PsA) share many treatments, including methotrexate, biologics, small molecules, and cyclosporine. Valenti et al described a case of psoriasis and PsA managed with adalimumab every 2 weeks for about 2 years, which rapidly recovered from COVID-19.[43] Messina et al reported a case of COVID-19 in a patient with psoriasis and PsA on guselkumab. The patient showed only mild symptoms and the authors suggested that IL-23/IL-17 pathway interference may not be harmful in the setting of COVID-19 infection.[36]

Although there is a slight risk of infections with these therapies, many rheumatologic societies including European League Against Rheumatism and American College of Rheumatology are against the improper withdrawal of immunosuppressants and immunomodulatory therapies for PsA due to the risk of disease flare, which may be associated with more adverse events than the treatment itself. Exacerbation of PsA may induce systemic inflammation and immunological disturbance, which are responsible for increased sensitivity to infections in the setting of systemic polyarthritis. Moreover, an active disorder requires a medical reassessment, which is best to be avoided during the pandemic due to the higher risk of contamination in the hospital. On the other hand, if any symptoms suggestive of COVID-19 occur, the discontinuation of immunosuppressive and immunomodulatory therapies should be considered on a case-by-case basis.[44] It should be noted that almost all available data originate from the pre-COVID-19 area and they should be interpreted with caution.[45]

Nonsteroid anti-inflammatory agents are also frequently used in PsA. WHO announced that there is no evidence of any relationship between the use of nonsteroid anti-inflammatory agents and COVID-19 mortality. Until more data are available, nonsteroid anti-inflammatory agents should not be discontinued in patients with PsA.[46]

3 | CONCLUSIONS

The COVID-19 pandemic has negatively affected the management of many diseases, and psoriasis is not exempt from this situation. Patients' inability to access adequate healthcare services and stress burden caused exacerbations in psoriasis cases. We believe that it is essential to closely monitor patients with psoriasis and provide alternative healthcare tools, such as telephone consultations and teledermatology, when necessary. Providing psychosocial support to the patients and their families may also have beneficial effects in controlling the disease activity. We recommend that classical immunosuppressive agents such as methotrexate, cyclosporine, and TNFα inhibitors should be avoided especially in high-risk areas. Considering that the current study has provided no conclusive evidence that biologics increase the risk of COVID-19, withdrawal of these agents should be reserved for patients with COVID-19 symptoms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Ö.F.E., A.D., Ö.K., and M.S.M. contributed to literature searching, designing, and writing the manuscript. Ö.F.E., F.B, M.A., Ü.T., and T.L. contributed to substantial contributions to conception, design, and interpretation of data. Ö.F.E., A.D., N.A., and K.Ö. contributed to editing, revising, and final approval of the manuscript.

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