Received: 12 September 2020 | Revised: 12 October 2020 | Accepted: 1 November 2020

DOI: 10.1111/dth.14507

REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Treatment considerations for Behçet disease in the era of COVID-19: A narrative review

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Abstract

COVID-19 is a multisystem disease caused by severe acute respiratory syndrome coronavirus 2. It has been declared a pandemic by the World Health Organization in March 2020 and the outbreak still keeps its impacts worldwide. Behçet disease (BD) is a multi-systemic vasculitis involving the skin, mucosa, eyes, joints, nervous system, cardiovascular system, and gastrointestinal system. The precise etiopathogenesis of the disorder is unknown but autoimmunity is believed to play a key role. A considerable part of patients with BD are susceptible to immunosuppression and are more predisposed to infections than healthy individuals. Hence, the protection and control measures for patients with BD against the COVID-19 are of the utmost significance. Given the requirement to balance proper treatment of BD with the smallest risk of COVID-19 associated mortality and morbidity, we aimed to review the management of BD in the era of the pandemic with a special focus on treatment considerations. According to current expert recommendations, there is no reason to discontinue topical treatments, colchicine, and nonsteroidal antiinflammatory drugs. Systemic steroids can be used at the lowest possible dose if needed. Ongoing treatments can be continued unchanged in patients with no suspected or confirmed COVID-19. In cases with COVID-19 symptoms, immunosuppressive and biological agents can be temporarily stopped but the decision should be made on a case by case basis. Considering their potential beneficial effects on the course of COVID-19, colchicine, pentoxifylline, and dapsone can be considered as safe treatment options in BD.

KEYWORDS

Behçet syndrome, colchicine, COVID-19, SARS-CoV-2

1 | INTRODUCTION

COVID-19 is a multisystem disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been declared a pandemic by the World Health Organization in March 2020 and the outbreak still keeps its impacts worldwide.[1] COVID-19 related mortality risk factors mainly include advanced age, male sex, and certain comorbidities, including immunosuppressive conditions.[2]

Behçet disease (BD) is a multi-systemic vasculitis affecting the skin, mucosa, eyes, joints, nervous system, cardiovascular system, and gastrointestinal system. The precise etiopathogenesis of the disorder is unknown but autoimmunity is believed to play a key role. The most frequent clinical presentation of BD is recurrent mucocutaneous ulcerations known as aphthosis. The other clinical signs differ among patients and populations. The disorder tends to be more severe in male patients. Ocular, vascular, and nervous system involvements are the main determinants of morbidity and mortality.[3]

COVID-19 crisis caused the postponement of many medical activities. This pandemic-caused obstruction in healthcare systems could restrict the diagnosis and management of many skin diseases. A considerable part of patients with BD are susceptible to immunosuppression and are more predisposed to infections than healthy individuals. Hence, the protection and control measures for patients with BD against the COVID-19 are of the utmost significance. To ensure the safety and effectiveness of treatment throughout the pandemic, physicians should keep their communication with patients, follow changes in patients' conditions, and adjust the treatment program, while protecting them against the COVID-19.

Given the requirement to balance proper treatment of BD with the smallest risk of COVID-19 associated mortality and morbidity, we aimed to review the management of BD in the era of the ongoing pandemic with a special focus on treatment considerations.

2 | METHODS

This narrative review includes searching PubMed, Google Scholar, and Web of Science databases using the keywords "Behçet disease," "Behçet syndrome," "coronavirus," "COVID 19," and "SARS-CoV-2." The search was supplemented by manual searching of the reference lists of included articles. The search was updated in September 2020. The guidelines provided by the American College of Rheumatology (ACR) task force, European League Against Rheumatism (EULAR) task force and, International Society for Behçet disease (ISBD) were also included.

3 | THE IMPACT OF COVID-19 ON THE COURSE OF BEHÇET DISEASE

It has not yet been known that patients with BD have an increased risk to be infected with SARS-CoV-2, compared to healthy people. However, this seems possible particularly for patients under immunosuppressive treatments. There are a limited number of studies investigating the course of BD in the era of COVID-19. In a Turkey-based study, 54 patients with BD admitted between 11 March and 14 July 2020 were retrospectively analyzed. The mean age of the patients was 32 years and 52% was female. The most common finding for these patients was oral ulcers followed by genital ulcers, papulopustular lesions, arthritis, uveitis, erythema nodosum, positive pathergy phenomenon, thrombophlebitis, epididymitis, extragenital ulcers, and central nervous system involvement. The most common treatment used was colchicine monotherapy (68.5%) followed by colchicine + azathioprine (7.4%), azathioprine only (7.4%), penicillin (5.6%), colchicine + systemic corticosteroid (3.7%), anti-TNF (3.7%), cyclosporin (1.9%), and dapsone (1.9%). Forty-four out of 54 patients were advised to maintain their ongoing treatment. The dosage of azathioprine and cyclosporine was reduced in seven patients, while the treatment of three patients was changed. The authors observed no serious activation and none of the patients contracted SARS-CoV-2 infection.[4]

In another Turkey-based study, the authors investigated a total of 10 BD patients with COVID-19 between 01 April and 21 May 2020. The median age of the patients was 39.5 years and the median disease duration was 15 years. In addition to mucocutaneous lesions, four patients had ocular involvement, one had both ocular and neurological involvement and one had large vessel disease. Except for one patient who was off treatment, all nine were on the following treatments either alone or in combination: colchicine (n = 5), azathioprine (n = 3), anti-TNF agents (n = 3) or prednisolone (n = 2). Three patients had comorbidities including epilepsy (n = 1), psoriasis (n = 1), and endometrium cancer (n = 1). All patients showed one or more COVID-19 related symptoms except one who was coincidentally diagnosed with severe COVID-19 pneumonia in the full-body computerized tomography (CT) scan. In total, 6 of 10 patients were diagnosed with COVID-19 pneumonia while four patients tested positive for SARS-CoV-2 with mild-to-moderate symptoms. Except for one patient who showed severe respiratory failure, none of the patients had respiratory distress. Eight patients were hospitalized and two of these were admitted to the intensive care unit. The median duration for hospitalization was 7 days. Six received a combination of hydroxychloroquine, oseltamivir, and azithromycin. Of these six patients, two additionally received systemic prednisolone. One patient received a combination of hydroxychloroquine, favipiravir, and enoxaparin while one patient received a combination of hydroxychloroquine and azithromycin. The remaining two patients received only hydroxychloroquine. The only patient with severe respiratory failure was a 38-year-old female with a 21 year history of BD. She was off-treatment for 3 years being clinically inactive and was on valproic acid since childhood due to grand mal epilepsy. The patient presented with fever and respiratory distress and managed along with a combination of hydroxychloroquine, oseltamivir, azithromycin, and favipiravir. She passed away due to severe respiratory failure 9 days after the diagnosis of COVID-19. Two patients developed de novo deep vein thrombosis short after having contracted COVID-19. Besides, three patients showed aggravations of oral ulcers or arthralgia. In their case series, the authors did not provide detailed information on whether they preferred to modify the ongoing treatments for BD.[5]

In a Spain-based study, the authors shared the main clinical characteristics of four patients with BD contracted SARS-CoV-2 infection. They reported that 2135 consecutive patients with COVID-19 were admitted to their center and of all patients, four (0.19%) had BD. The mean age of these patients with BD was 44 years and all were female. Only one patient had comorbidity (breast cancer). Three patients had an upper respiratory infection and one showed pneumonia. The severity of the infection was mild in all cases and no patient needed admission to the intensive care unit. In addition to the common manifestations of BD, one patient had a history of vascular manifestation while another one had neurologic manifestations. Disease activity calculated by Behçet Disease Activity Index at the time of first COVID-19 symptoms was low for all patients. At the time of admission, the first patient was on prednisolone (5 mg/day), and methotrexate (20 mg/day), the second patient was on colchicine (1 mg/day). The third patient was on prednisolone (7.5 mg/day), azathioprine

(100 mg/day), and colchicine (0.5 mg/day) while the fourth one was on pentoxifylline (400 mg/day) only. The second patient showed BD flare with oral ulcerations and erythema nodosum during the COVID-19 infection while the fourth patient had a flare 15 days after the COVID-19 infection with oral and genital aphthosis. In both patients, BD aggravation improved with colchicine.[6]

4 | TREATMENT CONSIDERATIONS FOR PATIENTS WITH BEHÇET DISEASE IN THE ERA OF COVID-19

4.1 | Local treatments

There is no reason to discontinue topical treatments in BD patients with or without COVID-19. Mild BD cases with only mucocutaneous involvement can safely be managed with topical treatments including topical corticosteroids, sucralfate, topical anesthetics, and topical antiseptics.

4.2 | Colchicine

Colchicine inhibits leukocyte functions and is commonly used for mucocutaneous and joint involvement with a dose of 1 to 2 mg/day. Colchicine is an anti-inflammatory agent inhibiting leukocyte functions and is commonly used for mucocutaneous and joint involvement with a dose of 1 to 2 mg/day.[3] It is generally accepted that colchicine does not increase the risk of infection. It has been suggested that colchicine may have a place in the treatment of COVID-19, considering its antiinflammatory properties with a relatively good adverse effect profile. Moreover, given its cardioprotective effects, it has been proposed that colchicine may prevent pericarditis and myocarditis, which are considered significant causes of mortality in COVID-19. ISBD has also advised not to discontinue Colchicine to prevent a relapse of the disease in BD patients with COVID-19.[7]

4.3 | Systemic corticosteroids

Systemic corticosteroids are broadly used in BD and may be effective in the short-term; nevertheless, long-term use is of great concern because of the adverse event profile including the risk of infections.[3] This concern has become more obvious in the era of the COVID-19 pandemic. The antiinflammatory properties of systemic corticosteroids attracted attention due to hyper-inflammation provoked by host immune responses in COVID-19. Notwithstanding the concerns that corticosteroids may disrupt viral clearance, studies showed they may have a role in the treatment of severe COVID-19.[8] ISBD has suggested that systemic corticosteroids at doses of 10 mg or less can be used in case of relapse in low and moderate risk conditions for COVID-19. ISBD has also recommended doubling the dose of corticosteroid in BD patients with COVID-19, taking into account adrenal stress and the possible benefits of corticosteroids.[9] (This recommendation is only for those at a dose of lower than 10 mg). The ACR has advised that the lowest possible dose of systemic corticosteroids can be used in rheumatic patients when necessary, regardless of COVID-19 exposure status.[10] EULAR has recommended maintaining ongoing corticosteroid therapy in rheumatic patients, regardless of the presence of COVID-19 symptoms.[11]

4.4 | Nonsteroidal antiinflammatory drugs

Nonsteroidal antiinflammatory agents may be helpful to control joint pain in BD.[3] Although speculation was raised early in the pandemic concerning NSAID use and potential relationships with more serious COVID-19 prognosis, these concerns have still to be verified.[12] The ACR task force recommended the maintained use of NSAID with the reservation that these agents should be discontinued in those with severe signs of COVID- 19, such as renal, cardiac, or gastrointestinal damages. Acetaminophen may be an alternative to NSAIDs in these circumstances although caution is necessary concerning possible hepatic injury accompanying COVID-19.[10] The EULAR task force concluded that NSAIDs can be used with no additional risk for worse COVID-19 prognosis and deserve no more particular mention in the recommendation.[11]

4.5 | Conventional immunosuppressive agents

The use of immunosuppressive treatment has unquestionably provided advancement in the management of severe BD. The main conventional immunosuppressive agents used in BD include azathioprine, cyclosporin A, methotrexate, and cyclophosphamide.[3]

Azathioprine has been shown to be beneficial in recalcitrant oral and genital aphthosis and is strongly recommended as the initial therapy for BD patients with inflammation of the posterior segment of the eye. Azathioprine has also been demonstrated to be effective for BD with vascular, neurologic, and intestinal involvement.[13] The use of azathioprine poses a moderate risk of serious infections and this risk is particularly high in elderly patients on long-term systemic corticosteroid therapy.[7] The use of cyclosporine is with a mild to moderate risk of upper respiratory tract infections. Nevertheless, hypertension and renal dysfunction associated with cyclosporine may pose a serious risk for patients with COVID-19.[7] Hypertension is considered to increase the rate of mortality and admission to intensive care in patients with COVID-19.[14] Methotrexate has been reported to be associated with an increased risk of pneumonia. Given that COVID-19 causes pneumonia, methotrexate can pose a particular risk.[7] Cyclophosphamide suppresses the bone marrow and may cause serious infections including pneumococcal pneumonia and herpes zoster. This risk is more prominent in patients with concurrent corticosteroid therapy.[7]

According to the ISBD, decreasing conventional immunosuppressive medications for BD patients with no symptoms of COVID-19

may be appropriate depending on a physician's decision, while discontinuation is advised in case of fever and/ or dyspnea or ARDS.[9] The ACR task force recommended that in the absence of infection or known SARS-CoV-2 exposure, ongoing immunosuppressant treatment may be continued but these drugs should be discontinued following known SARS-CoV-2 exposure and in the context of active or presumptive COVID-19.[10] The EULAR task force recommended that patients with rheumatic diseases with no suspected or confirmed COVID-19 should maintain their treatment unchanged, including immunosuppressive treatments. The task force further recommended that if patients with rheumatic diseases show mild symptoms of COVID-19, potential treatment changes in immunosuppressive agents should be discussed on a case-by-case basis. However, patients who are admitted to the hospital because of significant COVID-19 should follow local treatment advice as implemented by the treating expert.[11]

4.6 | Interferons

Interferons (IFNs) have antiviral, antiproliferative, and immunoregulatory activities and the efficacy of interferon α2a and α2b for mucocutaneous, ocular, and joint involvement has been demonstrated in different studies.[15,16] In an uncontrolled, exploratory study conducted on patients with COVID-19, IFN-α2b reduced the duration of detectable virus in the upper respiratory tract and elevated blood levels for the inflammatory markers.[17] Considering these preliminary results, IFNs can be considered as a safe option for recalcitrant cases of BD in the era of COVID-19; however, further studies are needed to reveal the exact effect of IFNs on the course of COVID-19.

4.7 | Anti-TNF agents

Several studies showed that biologic agents including etanercept, infliximab, and adalimumab are effective in reducing ocular inflammation and decreasing the frequency of uveitis attacks in patients with BD. These agents are also found to be effective in gastrointestinal, neurologic, vascular, joint, and mucocutaneous involvement.[3,18,19] Biologics are known to increase the risk of infection and patients under biologic agent therapy need careful monitoring due to some significant adverse effects. On the other hand, biologics inhibit proinflammatory cytokines and they may have the potential to offer protective effects against cytokine storm observed in COVID-19.[7] In this context, there are ongoing discussions as to whether these agents should be used during the pandemic. ISBD recommended that postponing biologicals may be appropriate depending on a physician's decision in high-risk situations. They further recommended that the continuation of a biologic agent in a patient with COVID-19 should depend primarily on whether it is utilized for a serious organ-threatening disease.[9] The EULAR task force suggested that patients with rheumatic diseases with no suspected or confirmed COVID-19 should be advised to maintain their treatment unchanged including biologic agents. The task force also recommended that potential treatment changes should be considered on a case-by-case basis for patients with suspected or confirmed COVID-19.[11] The ACR task force recommended that in the absence of infection or known SARS-CoV-2 exposure, ongoing treatment with non-IL-6 biologic agents can be maintained but these agents should be stopped following known SARS-CoV-2 exposure and in the context of active or presumptive COVID-19.[10]

4.8 | Dapsone

Dapsone has antimicrobial and antiinflammatory properties and is unlikely to increase the risk of infection. A double-blind controlled study revealed that dapsone may be an effective option in the treatment of mucocutaneous manifestations of BD.[20] Dapsone inhibits neutrophil chemotaxis through IL-8.[21] Considering that patients with acute respiratory distress syndrome have elevated levels of IL-8, it has been hypothesized that dapsone could be a potential therapeutic option for COVID-19.[22,23] Dapsone may be considered another safe option for BD patients with recalcitrant mucocutaneous manifestations in the era of COVID-19.

4.9 | Pentoxyphilline

Pentoxifylline, a nonselective phosphodiesterase inhibitor, is considered an immunomodulator and anti-inflammatory agent. It has known to reduce the levels of inflammatory mediators including TNF alpha, interleukin 1, interleukin 6, and interferon-gamma levels.[24] There are several reports suggesting pentoxifylline as a safe option in the management of mucocutaneous, ocular, and intestinal involvement of BD.[25-28] It has been hypothesized that pentoxifylline may also reduce tissue damage during the cytokine storm host response to SARS-CoV-2 infection.[24] Considering, its favorable profile of safety and tolerability, pentoxifylline may be considered a potential treatment option for the management of recalcitrant cases of BD in the era of COVID-19 pandemic. Safety considerations for the treatment of BD in the setting of the pandemic have been summarized in Table 1.

5 | CONCLUSIONS

To sum up, we believe that topical treatments, colchicine, and nonsteroidal anti-inflammatory drugs should not be discontinued for pandemic-related causes. Systemic steroids can be used at the lowest possible dose if needed. Ongoing treatments can be continued unchanged in patients with no suspected or confirmed COVID-19. In cases with COVID-19 symptoms, immunosuppressive and biological agents can be temporarily stopped but the decision should be made on a case by case basis. Considering their potential beneficial effects on the course of COVID-19, colchicine, pentoxifylline, and dapsone can be considered as safe treatment options.

TABLE 1 Safety considerations for the treatment of BD in the setting of COVID-19 pandemic

Topical treatments	No reason to discontinue topical treatments in BD patients with or without COVID-19. Topical agents are considered safe and effective in mild to moderate mucocutaneous involvement.
Colchicine	Colchicine does not increase the risk of infection and may have a place in the treatment of COVID-19, considering its anti-inflammatory properties with a relatively good adverse effect profile.
Systemic corticosteroids	The lowest possible dose of systemic corticosteroids can be used in BD patients when necessary, 10 mg/day or less doses are generally considered safe in the setting of COVID-19.
Nonsteroidal anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs can be used with no additional risk for worse COVID-19 prognosis.
Conventional immunosuppressive agents	Discontinuation of immunosuppressive agents should be discussed on a case-by-case basis in the setting of active or presumptive COVID-19.
Interferons	Considering the results of preliminary studies, interferons can be considered as a safe option for recalcitrant cases of BD in the era of COVID-19, however, further studies are needed to reveal the exact effect of interferons on the course of SARS-CoV-2 infection.
Anti-TNF agents	Postponing biologicals may be appropriate depending on a physician's decision in high-risk situations. The maintenance of biologic therapy in a patient with COVID-19 should depend primarily on whether it is utilized for a serious organ-threatening disease
Dapsone	Dapsone can be considered as a safe option for BD patients with recalcitrant mucocutaneous manifestations in the era of COVID-19.
Pentoxyphilline	Considering its favorable profile of safety and tolerability, pentoxifylline may be a potential treatment option in BD patients during the COVID-19 pandemic.

Abbreviation: BD, Behçet disease.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ömer Faruk Elmas, Abdullah Demirbaş, Fatih Bağcıer: Literature searching, designing and writing the manuscript. Ömer Faruk Elmas, Abdullah Demirbaş, Ümit Türsen, Mustafa Atasoy: Substantial contributions to conception and design, interpretation of data. Ömer Faruk Elmas, Abdullah Demirbaş, Recep Dursun, Torello Lotti: Editing, revising and final approval of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Elmas ÖF, Demirbaş A, Bağcıer F, et al. Treatment considerations for Behçet disease in the era of COVID-19: A narrative review. *Dermatologic Therapy*. 2021; 34:e14507. https://doi.org/10.1111/dth.14507