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Treatment of Skin and Mucosal Involvement of Behçet's Disease

Gülhan Gürel*

Department of Dermatology, Bozok University, Turkey

***Corresponding author:** Gülhan Gürel, Department of Dermatology, Medicine Faculty, Bozok University, Yozgat, Turkey; Email: gulhanozturkgurel@hotmail.com

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The treatment of Behçet's disease depends on various factors such as organ involvement, severity of involvement, recurrence frequency, duration of disease, age at onset of disease, and sex of the patient. However, the main goal of the treatment is to prevent irreversible organ damage, particularly in the early, active phase of the disease. Therefore, early and appropriate treatment is mandatory to reduce morbidity and mortality [1,2]. The main principle of treatment is the suppression of inflammation rapidly during acute exacerbations to prevent damage and relapses with immunosuppressive agents, if necessary [3].

TOPICAL TREATMENT

A significant part of experience in this area arises from the studies related to recurrent aphthous stomatitis. As it is known, the clinical appearance and course of oral ulcers of Behçet's disease is similar to recurrent aphthous stomatitis. Therefore, the recommended treatment approaches for recurrent aphthous stomatitis are also largely valid for the oral ulcers of Behçet's disease [1]. The treatment of mucocutaneous lesions usually depends on the severity of lesions. Topical measures are usually enough for isolated oral and genital ulcers [4]. The main goals of treatment are to shorten the duration of ulcer, reduce pain and increase disease-free periods, and the secondary goals are to reduce the frequency and severity of recurrences [5].

Topical Corticosteroids

Topical corticosteroids (i.e., betamethasone mouthwash, fluticasone propionate spray, and triamcinolone) are widely used in the treatment of active ulcers [1,6]. The goal of this treatment is to relieve the symptoms. Topical corticosteroids reduce pain, shorten the healing time of aphthae, and thus allow the patient to eat, speak, and perform oral hygiene. Triamcinolone acetonide is administered 3-10 times a day for 3-5 min at concentrations ranging from 0.05-0.5%. It is particularly indicated in patients with small and mild erosive lesions. To facilitate healing, it is recommended that the drug be administered directly to the lesions, kept in direct contact for as long as possible, and avoid food and fluid ingestion for 20 minutes after administration [6]. In particular, painful deep ulcers can be treated with a 0.1-0.5 mL intralesional triamcinolone suspension per lesion. Since the topical corticosteroids increase the possibility of oral candidiasis when used regularly, patients should be monitored carefully [7]. Although controlled studies are still insufficient, in clinical practice, potent corticosteroid ointments alone or in combination with antiseptics have been used successfully in the treatment of genital ulcers [1].

Antiseptic, Anti-Inflammatory and Analgesic Preparations

The first-line treatment options for oral ulcers are antiseptic and anti-inflammatory / analgesic medications, such as 0.2% chlorhexidine t.i.d. without swallowing. In patients with oral ulcer, 0.2% chlorhexidine administration is suitable to minimize the possibility of Gram-positive and Gram-negative bacteria and fungi. In addition, chlorhexidine has been shown to be effective against enveloped viruses such as herpes simplex virus, cytomegalovirus, and influenza and respiratory syncytial virus the *in vitro* setting [6,8]. It should be kept in mind that chlorhexidine users may experience bitter taste and brown discoloration in teeth and tongue as a side effect [9]. Triclosan t.i.d. can be used also in the form of gel or rinse without swallowing, as long as lesions persist, and it has anti-inflammatory, antiseptic and analgesic effects. In return, topical 3% diclofenac and 2.5% hyaluronic acid can be administered to reduce pain [6].

Topical Antibiotics

Topical antibiotics such as tetracycline and its derivatives (doxycycline and minocycline) are used for oral ulcer treatment in gel or rinse form. These drugs inhibit collagenases and metalloproteinases, which form a part of inflammatory response and contribute to tissue destruction and ulcer formation [10]. To avoid stabilization problems, the drug should be prepared by dissolving of 250 mg capsule in 10 ml of tap water just before use. The medication accelerates healing while reducing pain complaints [7]. In previous studies, minocycline-containing mouthwashes were found to be superior to placebo and tetracycline-containing mouthwashes, in reducing the severity and duration of pain in oral ulcers [11,12]. In recent years, 0.5% concentrations of minocycline have been found to be more effective than concentrations of 0.2% [13].

Sucralfate

Sucralfate is an agent which forms a protective barrier by locally binding to the proteins on the floor of the gastrointestinal tract ulcers. It stimulates mucus production and facilitates the binding of growth factors including epidermal growth factor. In addition, it activates nitric oxide and prostaglandin systems, which can contribute to the preservation of mucosal integrity and microcirculation. Sucralfate may play a role not only in the healing of damaged mucosa but also in the protection of mucosal surfaces due to its antioxidant effects [14]. Its efficacy has also been demonstrated in oral mucositis due to cancer chemotherapy in addition to oral ulcers and peptic ulcers [15]. In a previous study, it has been shown that sucralfate treatment significantly reduces the pain and healing time of oral and genital ulcers in Behçet's disease. In addition, in this study, the efficacy of sucralfate on the frequency and healing time of oral ulcers was sustained in the post-treatment period [16].

Amlexanox

Amlexanox is a drug that provides short-term efficacy, particularly when used in the prodromal stage. Although the mechanism of action is not known exactly, it is a topical agent thought to have anti-inflammatory and anti-allergic properties [10]. It is usually administered in the ointment form at a concentration of 5% and 2-4 times a day [17]. Studies have shown that amlexanox is effective in accelerating the healing of ulcer, and reducing pain, erythema and size of the lesions [18,19].

Other Treatments

In addition to the above-mentioned treatments, it has been observed that the administration of silver nitrate pencil once a day significantly reduces pain in oral ulcers [20]. In studies performed with laser applications such as CO2 laser, Nd: YAG laser and diode laser, it has been found to alleviate symptoms, accelerate wound healing and to have a lower risk of side effects in patients with oral ulcers [21,22]. In addition, natural products such as myrtle (*Myrtus communis*), quercetin, and Damask rose are also tested treatment options in oral ulcers [23-25].

Pimecrolimus can be used as a first-line topical treatment option in genital ulcers [26,27]. Although controlled studies are still insufficient, in clinical practice, corticosteroid ointments alone or in combination with antiseptics have been successfully used in the treatment of genital ulcers [1].

Erythema nodosum-like lesions are treated topically as classical erythema nodosum. Wet dressings (Burow solution, i.e. 3-5% aluminum acetate) can be applied in the early stage of lesions. Similar application is also effective in superficial thrombophlebitis [28].

The topical therapeutic agents used in the treatment of mucocutaneous findings of Behçet's disease are shown in Table 1.

Table 1: Topical therapeutic agents used in the treatment of mucocutaneous manifestations of Behçet's disease.

1.	Topical Corticosteroids (Betamethasone, fluticasone propionate, triamcinolone acetonide)
2.	Antiseptic, antiinflammatory and analgesic preparations (Chlorhexidine, triclosan, diclofenac)
3.	Topical antibiotics (Tetracycline, doxycycline and minocycline)
4.	Sucralfate
5.	Amlexanox
6.	Other treatments (Silver nitrate, CO2 laser, Nd: YAG laser and diode laser, myrtle, quercetin, damask rose, pimecrolimus)

SYSTEMIC TREATMENT

The systemic therapeutic agents used in the treatment of mucocutaneous findings of Behçet's disease are shown in Table 2.

Table 2: Systemic therapeutic agents used in the treatment of mucocutaneous manifestations of Behçet's disease.

1.	Colchicine ± benzathine penicillin
2.	Systemic corticosteroids
3.	Dapson
4.	Azathioprine
5.	Cyclosporin
6.	Thalidomide
7.	Interferon alpha
8.	Anti TNF alpha inhibitors (Infliximab, adalimumab, etanercept)
9.	Phosphodiesterase 4 inhibitors (Apremilast)
10.	Interleukin-1 inhibitors (anakinra, canakinumab and gevokizumab)
11.	Other treatments (Rebamipide, pentoxifylline)

Colchicine

Colchicine is used in the treatment of Behçet's disease, particularly with mucocutaneous involvement. The anti-inflammatory effect of colchicine is mediated by disruption of microtubules in the neutrophils, thus, inhibition of migration to chemotactic factors [2]. The first option in the treatment of oral ulcers, genital ulcers, erythema nodosum-like lesions and superficial thrombophlebitis is colchicine. In a double-blind placebo-controlled study including patients with mucocutaneous symptoms, when female and male patients were evaluated separately, it has been found to reduce the frequency of genital ulcer, and be effective in the treatment of erythema nodosum and arthritis in female patients using colchicine for two years. It has been found to be effective in arthritis treatment in males [29]. In a subsequent double-blind placebo-controlled study, it has been observed that colchicine significantly reduced the disease activity index score [30]. If the efficacy of colchicine alone is insufficient, it can be combined with benzathine

penicillin [1]. After the cessation of colchicine treatment, contraception is recommended for 3 months in females and for 6 months in males. More than 45% of patients using colchicine report gastrointestinal complaints [7]. Significant gastrointestinal intolerance may develop, when the drug is used at doses higher than 1.5 mg/day [2].

Systemic Corticosteroids

Although systemic corticosteroids are widely used in the treatment of Behçet's disease, there is only one placebo-controlled randomized study. A total of 86 patients with active disease and genital ulcer have been included in the study. Methylprednisolone (40 mg, i.m.) or placebo has been administered to the groups in every 3 weeks for 27 weeks. There were no significant differences in terms of mean number of oral ulcer, genital ulcer and folliculitis between the groups, but the number of erythema nodosum-like lesions was lower in the corticosteroid group, particularly in female patients [31]. During acute exacerbations of oral ulcer, genital ulcer, erythema nodosum-like lesions and superficial thrombophlebitis, short-term systemic corticosteroids together with drugs such as colchicine may be used as an alternative treatment [1].

Dapsone

Similar to colchicine, it exhibits activity by inhibiting increased chemotaxis activity in neutrophils. In the controlled study of Sharquie et al., [32] significant efficacy has been observed in oral ulcers and genital ulcers, as well as in erythema nodosum-like lesions and papulopustular lesions compared to placebo.

Azathioprine

Azathioprine is a drug with immunosuppressive effects that inhibits purine synthesis, which is commonly used in the treatment of Behçet's disease [2]. In the only placebo-controlled study, azathioprine at a dose of 2.5 mg/kg/day has been shown to be effective in the treatment of oral ulcer, genital ulcer and thrombophlebitis in addition to eye symptoms and arthritis [33]. Since the drug prevents the development of new ocular exacerbations, it can be used as an appropriate option in young male patients presenting with mucocutaneous symptoms.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that affects the proliferation of both T cells and B cells and is commonly used in the treatment of uveitis associated with Behçet's disease [2]. It has been observed in studies that it is more effective than conventional treatments in oral ulcers, genital ulcers, cutaneous lesions and superficial thrombophlebitis (as in joint and neurological symptoms) [1,3].

Thalidomide

Thalidomide was developed as a sedative drug in the 1950s and was withdrawn in 1961 due to its teratogenic effects. However, recently, it was rediscovered as an immunomodulatory drug

which suppresses tumor necrosis factor (**TNF**)-α induced nuclear factor (**NF**) -BB activation and adenosine triphosphate induced interleukin (**IL**) -1β secretion [34]. Thalidomide has been reported to be effective in the treatment of Behçet's disease with mucocutaneous lesions [35,36]. In the only double-blind, placebo-controlled study, it was used in 96 patients with Behçet's at doses of 100 mg and 300 mg, and has been observed to be effective in the control of oral ulcers, genital ulcers and papulopustular manifestations, and to prevent new lesion formation during use, but to increase erythema nodosum-like lesions. It has been observed that the symptoms of the disease were recurred after the drug was discontinued. While there has been no difference in clinical improvements among patients with two different doses, the sedation effect has been observed to be greater at higher doses [36].

Interferon Alpha

Interferon alpha (**INF-α**), 6 million IU/3 times a week for 3 months, is a naturally occurring cytokine with immunoregulatory, anti-proliferative and anti-neoplastic properties. INF-α, well known for viral diseases such as herpes and hepatic infections, increases the activity of T lymphocytes and natural killer cells which are impaired in Behçet's disease and also inhibits IL-8 production [37]. In Behçet's disease, it has been demonstrated in a randomized, placebo-controlled, double-blind study that INF alpha 2a reduces the duration and pain of oral ulcers, and reduces the frequency of genital ulcers, papulopustular lesions and erythema nodosum-like lesions [38]. Side effects related to the use of INF-α are common. It is easy to prevent flu-like syndrome with paracetamol, which is observed in almost all patients. In addition, conditions such as depression, asthenia, cytopenia and to a lesser extent psoriasis and sarcoidosis may be induced or worsened [39].

Anti TNF Alpha Inhibitors

TNF-α is a cytokine which is produced by T helper cells that mediates the inflammatory response in Behçet's disease [37,39]. TNF-α antagonists (infliximab, adalimumab, etanercept) may be preferred in patients with Behçet's disease with severe mucocutaneous findings resistant to steroid, colchicine, dapsone, azathioprine or thalidomide treatments [1,39]. Infliximab, a human chimeric monoclonal anti-TNF-α antibody, has been a therapeutic option in a few case reports of refractory mucocutaneous lesions. In two clinical cases with genital ulcer resistant to azathioprine and prednisone treatments, patients achieved complete remission with infliximab (5 mg/kg, a total of 4 infusions) [40,41]. Thus, infliximab provides good and long-term remission in mucocutaneous lesions even after cessation in the 13th infusion, as described in two clinical cases [42,43].

Etanercept is a dimeric fusion protein of the Fc portion of human IgG1 [37]. In a recent study, researchers obtained a good therapeutic response after 12 months of etanercept treatment (50 mg/week) in addition to conventional immunosuppressive drugs (azathioprine and colchicine) in patients with resistant mucocutaneous lesions [44]. In a randomized controlled trial, etanercept

has been shown to be effective in suppressing most of the mucocutaneous lesions such as oral ulcers, papulopustular lesions and nodular lesions, and to reduce the recurrence in oral ulcers [45]. Adalimumab, a completely human monoclonal anti-TNF-α antibody, has been determined in a recent multi-center retrospective study as an effective and safe treatment in patients with Behçet's disease with a broad clinical picture [46]. Adalimumab seems to be a useful treatment in oral ulcers (at doses of 40 mg every two weeks), although further research is needed to demonstrate the efficacy and tolerability [47].

Phosphodiesterase 4 Inhibitors

Apremilast is a new, oral phosphodiesterase 4 inhibitor which is currently approved for the treatment of psoriasis and psoriatic arthritis [48]. The efficacy of apremilast in oral ulcer treatment has recently been demonstrated in a double-blind, placebo-controlled, phase 2 study. In the study, it has been determined that oral ulcer was suppressed from the 2nd week and the pain score decreased significantly in the apremilast group. However, the efficacy of apremilast did not continue after the drug was discontinued, and the number of oral ulcers began to increase within 2 weeks after treatment. Gastrointestinal side effects such as nausea, vomiting and diarrhea were more common in apremilast than in placebo [49]. Currently, although apremilast seems to be a promising drug in the treatment of oral ulcers, the efficacy of apremilast in other organ involvements is still unclear [48].

Interleukin-1 Inhibitors

IL-1 has been recently described as a mediator in the pathophysiology of Behçet's disease. This innovative concept has enabled the identification of new potential targets for biological therapy [50]. Until now, 3 anti-IL-1 agents have been tested in Behçet's disease. These include anakinra, an IL-1 receptor antagonist, canakinumab, an anti-IL-1β monoclonal antibody, and gevokizumab, a recombinant humanized anti-IL-1β [51]. Case reports and series have shown the efficacy of IL-1 blockade in mucocutaneous disease [52-54]. Recently, a pilot open-label study has been conducted to evaluate the safety and efficacy of anakinra in the management of oral and genital ulcers in an American patient group with refractory mucocutaneous findings. In the study, it has been observed that Anakinra at an optimal dose of 200 mg daily have an acceptable safety profile and is partially effective in the treatment of resistant oral and genital ulcers in Behçet's disease [55]. In a small case series of patients with refractory mucocutaneous disease, rapid and continuous response to canakinumab has been reported in all patients [52]. In addition, despite promising results with gevokizumab in inflammatory eye disease, one study has revealed significant mucocutaneous exacerbations in patients [56].

Other Treatments

Rebamipide: Rebamipide, a gastroprotective agent, has been shown to provide a reduction in the frequency of aphthae and pain score compared to placebo in a double-blind placebo-controlled study at doses of 300 mg/day [57].

Pentoxifylline: Pentoxifylline inhibits the production and function of various proinflammatory cytokines, primarily TNF-alpha, and has anti-oxidative effects, and is effective in the treatment of oral and genital ulcers. It can be used as monotherapy or in combination with colchicine [37,58].

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