

# Managing Behçet's disease: An update on current and emerging treatment options

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**Abstract:** Behçet's disease is an autoinflammatory vasculitis of unknown origin characterized by recurrent oral and genital ulcers, uveitis, arthritis and skin lesions. Additionally, involvement of the gastrointestinal tract, central nervous system and large vessels may occur. The disease is prevalent in countries along the ancient Silk Road from Eastern Asia to the Mediterranean Basin. Many treatment modalities are currently available. The choice of treatment depends on organ involvement and severity of disease. Topical treatment with corticosteroids is often sufficient for mucocutaneous involvement, however for more severe disease with vasculitis or neurological involvement a more aggressive approach is warranted. Newer drugs (biologicals) influencing cytokines and thereby T-cell function are promising with an acceptable side effect profile. Unfortunately, reimbursement of the costs of biologicals for rare disease is still a problem in various countries. In this report we discuss the current treatment modalities for Behçet's disease.

**Keywords:** Behçet's disease, biologicals, treatment

## Introduction

Behçet's disease is an inflammatory disorder characterized by recurrent oral and genital ulcers, uveitis, and skin lesions.<sup>1,2</sup> The first series of patients with Behçet's disease was already published in 1937 as a triad of these symptoms.<sup>3</sup> Additionally, involvement of the gastrointestinal tract, central nervous system, and large vessels may occur, although less frequently. As in other immune-mediated disorders, Behçet's disease is characterized by attacks rather than by a persistent inflammatory disease.<sup>4</sup>

Cases of Behçet's disease cluster along the ancient Silk Road, which extends from eastern Asia to the Mediterranean basin. The reported prevalence in Turkey varies between 110 and 420 per 100,000.<sup>5</sup> In Western countries however the prevalence is probably less than 1 per 100,000 in Caucasians. It is believed that both genetic and environmental factors contribute to the development of the disease.<sup>6,7</sup> Men are affected slightly more often than women.

Susceptibility to Behçet's disease is strongly associated with the presence of the human leukocyte antigen (HLA)-B51 allele and its presence is also strongly associated with a more aggressive course.<sup>8</sup> The cause of Behçet's disease is however still unknown. Infections, both viral and bacterial, may play a role.

Although the exact cause of Behçet's disease remains to be elucidated, it is clear that neutrophils interacting with T-cells play an important role in the pathophysiology. Activated T-cells produce tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which in turn leads to production of other proinflammatory cytokines like interleukin-1 (IL-1) and IL-6

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by other immune cells. These proinflammatory cytokines stimulate migration and activation of leucocytes, thereby causing a local inflammatory response.<sup>2</sup> A disturbed function of regulatory T-cell may also play a role. Eventually vessel damage occurs, as can be seen in biopsies taken from Behçet's lesions from various sites involved.<sup>4</sup>

## Clinical picture

### Diagnosis

Currently the diagnosis of Behçet's disease is often based on the criteria as proposed by the International Study Group for Behçet's disease in 1990.<sup>9</sup> To fulfil these criteria, recurrent oral ulcers must be present together with two or more of the following; recurrent genital ulceration, eye lesions, skin lesions, or a positive pathergy test (Table 1). This test consists of pricking a sterile 20G needle into the patient's forearm. The results are judged to be positive when the puncture causes an aseptic erythematous nodule or pustule that is more than 2 mm in diameter at 24 to 48 hours. At the reaction site there is initially an accumulation of neutrophils followed by the accumulation of mononuclear cells.<sup>10</sup> The pathergy test is sometimes considered pathognomonic for the disease but can also be positive in other diseases like pyoderma gangrenosum.<sup>11</sup>

### Clinical manifestations

As mentioned above, all patients have recurrent oral aphthous ulceration at some time in the clinical course. Recurrent oral ulceration is often the presenting sign. Lesions are painful, last about 10 days, and heal without scarring. Genital ulcers are also painful, but often heal with scarring.

Ocular involvement is common and occurs in approximately 70% of patients and is associated with a high risk of blindness. Ocular features of Behçet's disease are anterior

uveitis, retinal vasculitis (both veins and arteries), optic neuropathy, retinal infiltrates, and vitritis.<sup>2</sup>

Various types of skin involvement can be seen. Erythema nodosum occurs frequently and is more common in women. Pseudofolliculitis and acneiform nodules are more common in male patients and are distributed on the back, face, and neck, especially along the hairline.<sup>2</sup>

The features of Behçet's disease, however, are not limited to the diagnostic criteria. The syndrome can present in a myriad of ways and may involve nearly every organ system. In fact, morbidity and mortality predominantly result from vasculitis in large vessels, cerebrovascular disease, and gastrointestinal involvement. The latter is often difficult to distinguish from Crohn's disease.<sup>2</sup>

### Current treatment options

First of all we must state that unfortunately the level of evidence is limited in most of the treatment regimens in Behçet's disease since there are few randomized controlled trials.

Treatment of patients with Behçet's disease is guided by organ involvement (Table 2). Topical steroids are usually effective for mucocutaneous involvement. Some patients respond insufficiently and additional treatment may be necessary in these cases. Colchicine is often believed to be effective for refractory oral ulcers. A double-blind study conducted in 1980 did not show a statistically significant reduction in the recurrence of both oral and genital ulcers compared to placebo.<sup>12,13</sup> In a double-blind trial with 116 patients in 2001, Yurdakul and colleagues found that colchicine reduced the occurrence of genital ulcers and erythema nodosum and arthritis in both men and women.<sup>14</sup> Perhaps colchicine is more effective in women than in men. Thalidomide has also been shown to be effective in patients with mucocutaneous lesions refractory to treatment with colchicine. Thalidomide exerts

**Table 1** International study group criteria for Behçet's disease

| Finding                      | Definition   |
|------------------------------|--|
| Recurrent oral ulceration    | Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period  |
| Recurrent genital ulceration | Aphthous ulceration or scarring observed by the physician or patient   |
| Eye lesions                  | Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist   |
| Skin lesions                 | Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a post-adolescent patient who is not receiving corticosteroids |
| Positive pathergy test       | Test interpreted as positive by the physician at 24 to 48 hours  |

**Table 2** Current treatment used for Behçet's disease

| Medication             | Dose  | Main indications   |
|------------------------|---|--|
| Prednisone             | Local systemic: 0.5–1 mg/kg   | Uveitis, Mucocutaneous involvement, Induction treatment uveitis, Neurological involvement<br>Refractory arthritis, Gastrointestinal ulceration |
| Colchicine             | 0.5–1.5 mg/day  | Skin involvement, Arthritis  |
| Dapsone                | 100 mg/day  | Mucocutaneous involvement Arthritis  |
| Azathioprine           | 2–3 mg/kg/day   | Uveitis  |
| Pentoxifylline         | 1200 mg/day   | Mucocutaneous involvement  |
| Sulfasalazine          | 1–3 g/day   | Mucocutaneous involvement, Arthritis   |
| Thalidomide            | 100–200 mg/day  | Refractory mucocutaneous involvement   |
| Cyclosporine           | 3–5 mg/kg/day in divided doses  | Uveitis, Mucocutaneous involvement   |
| Methotrexate           | 7.5–15 mg/week  | Arthritis, uveitis (rarely)  |
| Cyclophosphamide       | 750 mg/m <sup>2</sup> /mo IV  | Life-threatening involvement (vasculitis, neurological)  |
| IFN- $\alpha$ 2a       | 9 million units three times per week for three months followed by a low maintenance dose of 3 million units three times per week) | Uveitis  |
| TNF- $\alpha$ blockers | Various doses   | Uveitis Arthritis Gastrointestinal ulceration  |

**Abbreviations:** IFN, interferon; TNF, tumor necrosis factor.

considerable side effects (neuropathy, constipation) and for obvious reasons should be avoided in women with childbearing potential unless they adhere to stringent contraceptive measures. Pentoxifylline, which reduces the production of inflammatory cytokines like TNF- $\alpha$ , was effective in reducing the frequency and severity of oral and vaginal ulcers.<sup>15</sup> Alternative treatment for mucocutaneous involvement are dapsone<sup>16</sup> and cyclosporine. Cyclosporine is used infrequently for this indication for fear of side effects.<sup>17</sup> Nevertheless, cyclosporine resulted in significantly more alleviation of oral aphthous ulcers versus colchicine in a study by Masuda and colleagues.<sup>18</sup>

If there is only mucocutaneous involvement, locally applied corticosteroids may suffice. However, involvement of internal organs or brain may require much more aggressive treatment consisting of systemic corticosteroids of >1 mg/kg/day and immunosuppressive drugs. Sulfasalazine is mainly effective in arthritis and gastrointestinal involvement.<sup>4,19</sup> Azathioprine and cyclosporine are considered effective treatment especially in uveitis. Azathioprine has also been used in the treatment of neurologic and gastrointestinal involvement. Azathioprine and cyclosporine are often used in combination.<sup>19</sup> One of the newer immunosuppressive drugs, mycophenolic acid derivatives, although not effective in mucocutaneous lesions,<sup>20</sup> can be effective in therapy refractory gastrointestinal involvement.<sup>21</sup>

Vasculitis (large vessel) especially, often involving the pulmonary arteries and neurological disease, calls for

intensive measures as they can be life-threatening. In these cases, the use of cyclophosphamide alone or in combination with prednisone is warranted.<sup>22,23</sup> In life-threatening situations, cyclophosphamide should not be used without corticosteroids.

Interestingly, although the cause of Behçet's disease is unknown, treatment with high dose penicillin either alone or in combination with colchicine was effective in reducing symptoms (mucocutaneous and joint manifestations) in several studies. A possible role for streptococcal infection has been proposed.<sup>24–26</sup>

In some patients these therapies are either ineffective or are associated with intolerable adverse effects necessitating alternative treatment strategies. In the slipstream of the therapeutic management of rheumatoid arthritis, interesting agents targeting the factors believed to be involved in the pathogenesis of Behçet's disease have been tried in these patients with sometimes astonishing results.

## Emerging treatment options

As mentioned above, T-cells and cytokines are believed to play an important role in the pathogenesis of Behçet's disease. Emerging therapies aim at influencing T-cell function or cytokines.

### Interferon-alpha

Perhaps interferon-alpha (IFN- $\alpha$ ) no longer deserves to be called an emerging therapy as it has been used for therapy in

refractory Behçet's disease for over ten years.<sup>27</sup> IFN- $\alpha$  has been reported to restore the low natural killer cell activity in patients with Behçet disease to a near normal level. A double-blind study assigned 50 patients to receive either IFN- $\alpha$ 2Aa (6 million units three times weekly) or placebo for three months.<sup>28</sup> Significant decreases in pain and duration of oral ulcers, frequency of genital lesions, and number of pustular papules were noted in patients receiving IFN- $\alpha$ 2a. The frequency and duration of erythema nodosum-like lesions and thrombophlebitis were also decreased in the same group. In a systematic review of 32 studies and four published abstracts published before 2002, a total of 338 patients received either IFN- $\alpha$ 2a or 2b of various doses.<sup>29</sup> Within a few months of therapy, 86% of the patients with mucocutaneous symptoms, 96% with arthritis, and 94% with uveitis exhibited a partial or complete response. Significant improvements were also found in erythema nodosum-like lesions, skin ulcerations, and superficial thrombophlebitis. Interferon- $\alpha$ 2a seems to be more efficacious than IFN- $\alpha$ 2b. Compared with low-dose regimens, high-dose regimens were more effective and achieved more post-treatment remissions. However, disease activity generally returned to baseline level either immediately after or up to seven months after therapy was discontinued. Side effects of IFN- $\alpha$  include mild alopecia, mild leukopenia (generally reversible with discontinuing interferon), influenza-like symptoms, and depression or psychosis. The recommended regimen is a high dose of IFN- $\alpha$ -2a (9 million units three times per week) for three months followed by a low maintenance dose (3 million units three times per week).

### TNF blockers

TNF blockers represent a novel regimen of drugs in the treatment of Behçet's disease in which Th-1 proinflammatory cytokines such as IL-1- $\beta$ , IFN- $\gamma$ , IL-12, and TNF- $\alpha$  are involved in the inflammatory response that is held responsible for disease-related symptoms. It is believed that TNF- $\alpha$  plays a central role in the inflammatory process of Behçet's disease. Infliximab is a chimeric TNF- $\alpha$  antibody that has been reported effective in more than 10 small studies of a total of more than 120 patients and 115 other single Behçet's disease cases of refractory mucocutaneous lesions, severe gastrointestinal or neurological involvement, and ocular disease. One of the most significant studies was published in 2004 by Sfikakis and colleagues.<sup>30</sup> In this study, 25 patients with ocular disease were treated with a single infusion of 5 mg/kg infliximab. In all but one patient ocular inflammation was controlled within one day. In general,

remarkable and swift improvement or complete resolution of the orogenital ulcers, gastrointestinal ulcerations, and other Behçet's disease-related symptoms can be achieved shortly after one or two infusions of infliximab at various doses ranging from 3–10 mg/kg. A dose of 300–500 mg is generally accepted effective, but the time of interval and duration of therapy remain undetermined. In patients with acute, unilateral, posterior uveitis and significant reduction of visual acuity ( $<0.2$ ), as well as in those cases with inflammation of the macular area, a single infusion of infliximab, or intravitreal steroids may be superior to other immunosuppressive drugs. In cases of bilateral posterior eye segment inflammation, a single infusion of infliximab could be used as a first-line agent to achieve a fast-onset response, along with the initiation of other immunosuppressive drugs. However, if the ocular disease remains uncontrolled, a combination of immunosuppressive regimens with repetitive infusions of infliximab 5 mg/kg every 6–8 weeks for up to two years can be used.

Another TNF- $\alpha$  blocker used in Behçet's disease is the fusion protein, etanercept. One double-blind, placebo-controlled study has been conducted by Melikoglu and colleagues.<sup>31</sup> This study involved 40 male patients with mainly mucocutaneous disease randomly treated with either four weeks of 25 mg etanercept (subcutaneously twice a week) or placebo. Significant improvements of oral ulcers and nodular and papulopustular lesions were observed in the etanercept group. Within four weeks, 45% of the etanercept group remained free of oral ulcers compared with only 5% in the placebo group. No significant improvement in genital ulcers or pathergy positivity was observed. Eighty-five percent of the patients receiving etanercept were free of nodular lesions compared with 25% of those in the placebo group. Most patients experienced recurrent disease three months after etanercept was stopped. Other case reports included less than 10 Behçet's disease patients successfully treated with etanercept.

Even fewer studies were performed with adalimumab, a human TNF- $\alpha$  antibody. In 2006, two groups reported nine refractory Behçet's disease patients. In both retrospective studies, various symptoms in all patients resolved swiftly and persistently.<sup>32,33</sup> Adalimumab could be given for at least three years without serious adverse effects. The role of TNF blockers in patients with uveitis is currently accepted for selected cases. Although reportedly very effective in Behçet's disease, the place of TNF- $\alpha$  blockers in the therapeutic strategy, its long-term effects, and the timing of intervals still need to be investigated in more robust and fully powered

randomized trials. TNF blockers should be started as add-on strategy in combination with other drugs.

### Anti-IL-1 and anti-IL-6

Apart from TNF- $\alpha$ , other cytokines such as IL-1 and IL-6 may play a role in the disease. Some studies report significantly higher IL-1 levels in patients with both active and inactive Behçet's disease compared to controls, although this is not a universal finding. A recent case report describes a patient with refractory Behçet's disease responding rapidly to treatment with daily anti-IL-1. Lowering the dose to alternate day injections led to an increase in disease activity, again responding to an increase in the dose.<sup>34</sup>

IL-6 levels have been reported to be elevated in the cerebrospinal fluid of patients with active neuro-Behçet's disease. IL-6 has a major role in growth and differentiation of T cells, antibody production by B cells, and differentiation of macrophages. Inhibition of IL-6 signaling could be a new therapeutic regimen for neuro-Behçet's disease.<sup>35</sup> Tocilizumab is a humanized monoclonal antibody that binds both to soluble and to membrane-bound IL-6 receptor and has been shown to be effective in rheumatoid arthritis. This drug may potentially have an effect in Behçet's disease. However, data on treatment are lacking so far.

### Conclusions

Nowadays, many treatment options have become available for Behçet's disease. Few have been examined in double-blind trials and most treatments aim to relieve symptoms rather than cure the disease. Treatment should be tailored depending on the severity of disease. Newer drugs (biologics) influencing cytokines and thereby T-cell function are promising without very many side effects. Unfortunately, biologics are still expensive and long-term effects are still unknown.

### Disclosure

The authors report no conflicts of interest in this work.

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