Treatment of Behçet's disease

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Behçet's disease is a chronic, relapsing, systemic vasculitis of unknown etiology with the clinical features of mucocutaneous lesions and ocular, vascular, articular, gastrointestinal, urogenital, pulmonary and neurologic involvement. The disease is particularly prevalent in 'Silk Route' populations but has a global distribution. Behçet's disease effects primarily young subjects. The diagnosis is based on clinical criteria, as there is no pathognomonic test. Besides considerable morbidity, the disease confers an increased mortality, mainly due to large vessel (especially pulmonary arterial) and neurologic involvement as well as bowel perforation. No standard therapy has yet been established for the treatment of Behçet's disease, and a wide spectrum of therapeutic agents have been used with varying success. Treatment of the disease has become much more effective in recent years with the introduction of newer drugs. This paper will aim to provide an overview of the therapeutic approaches including local and systemic agents for the treatment of Behçet's disease.

Behçet's disease (BD) is a chronic, relapsing, systemic vasculitis of unknown etiology. The disease was first described in 1937 by Hulusi Behçet as a trisymptom complex, characterized by recurrent oral ulcers (OUs), genital ulcers (GUs) and uveitis [1]. Later studies have shown BD to be a multisystemic inflammatory disease with vascular, articular, gastrointestinal (GI), renal and neurologic involvement [2,3].

The disease usually starts around the third decade of life [4]. Recent epidemiologic surveys suggest that sex distribution is roughly equal in BD [5–7]. Serious organ involvement such as neurologic and large vessel involvement, eye diseases, folliculitis and thrombophlebitis, are more frequent in males [8,9].

The prevalence of the disease shows important geographic variations. The disease is much more frequent along the ancient 'Silk Route' extending from Eastern Asia to the Mediterranean basin, compared with Western countries. The prevalence of BD in Turkey is found to be almost 1 in 250 of the population aged 16 years or older [5], whereas that in the UK is less than 1 in 100,000 [10]. This marked geographic variation of BD can be explained by the genetic basis of the disease and/or environmental triggers. Genetic factors have been investigated extensively. Familial aggregation studies in patients with BD indicate a strong genetic background and a complex inheritance model. Several studies have demonstrated a significant association and an increased incidence of *HLA-B*$_{51}$ [11]. However, the presence of *HLA-B*$_{51}$ alone is not sufficient to explain all of the symptoms observed in BD and in agreement with this, recent studies suggest the involvement of other genes [2]. Overexpression of proinflammatory cytokines (mainly T-helper [Th] cell type 1) from various cellular sources appears to be responsible for the enhanced inflammatory reaction in BD and may be associated with genetic susceptibility [12]. Affected organs in patients with BD show significant neutrophil and lymphocyte infiltration. It is believed that the stimulated lymphocytes contribute to neutrophil and endothelial cell activation in these patients [13]. It has also been demonstrated that the sera of patients with BD induces classical (proinflammatory) activation of human peripheral-blood macrophages [14]. Several gene polymorphisms including interleukin *(IL)-1* [15,16], tumor necrosis factor *(TNF)*-α [17], intercellular adhesion molecule *(ICAM)-1* [18] and cytotoxic T lymphocyte-associated antigen *(CTLA)-4* [13] were shown to be associated with susceptibility to BD. Antigens derived from infectious agents, such as *Streptococci* and immunologic cross-reaction with heat shock proteins (HSPs) are also considered to play roles in the etiopathogenesis [19,20].

Clinical features

Mucocutaneous lesions

Mucocutaneous lesions constitute the hallmark of the disease. The high frequency of OUs and GUs and cutaneous lesions at any time in the course of the disease, or as onset signs, confirm the importance of these clinical features for diagnosis. OUs

Keywords: Behçet's disease, genital ulcer, oral ulcer, systemic vasculitis, treatment

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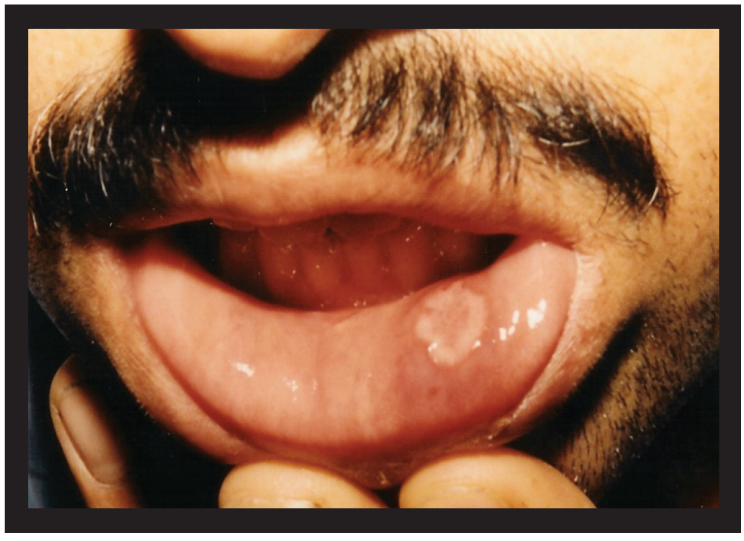
(92–100%), GUs (57–93%) and cutaneous lesions (38–99%) together with ocular and articular involvements, are the most frequent features of the disease in all countries [10]. OUs represent a feature of disease onset in the majority of patients worldwide (47–86%). GUs (0–18%) and cutaneous lesions, especially erythema nodosum-like lesions (0–19%), have also been reported as onset lesions [10]. In a recent study, we have shown that OUs (85%), GUs (21.7%) and articular symptoms (16.7%) were the most common onset manifestations, and synchronous onset of the clinical manifestations (OUs and GUs – 15%, and OUs and articular symptoms 10%) is not an uncommon feature of the disease [21].

Oral ulcers

OUs are characterized by recurrent and usually painful ulcerations of the oral mucosa. The most common sites of the lesions are the mucous membranes of the lips, buccal mucosa, under surface of the tongue and floor of the mouth. Patients may have single or multiple ulcers which often subside spontaneously after a couple of weeks and recur at intervals from days to months. They are identical to aphthae in appearance; however, they tend to be more frequent and multiple. The lesions start as an erythematous, slightly raised area evolving into an oval or round ulcer within 48 h with rolled or overhanging borders and a grayish-yellow necrotic base (**Figure 1**). An erythematous halo of inflamed mucosa surrounds the crateriform base of the ulcer [10,22]. They can be classified as minor, major or herpetiform on the basis of ulcer size and number. Minor ulcers, which are the most common, are either isolated or multiple shallow ulcers, less than 1 cm. They usually heal in 1 to 2 weeks without scarring. Major ulcers are morphologically similar to minor ulcers; however, they are larger (>1 cm), deeper, and more painful. These ulcers last longer and frequently heal with scarring and tissue loss. Generally a few ulcers occur at one time and they heal slowly over 10 to 40 days. Herpetiform ulcers are numerous (up to 100), shallow, small, pinpoint (1–2 mm in diameter) ulcers occurring in coalescing clusters. Occasionally herpetiform ulcers increase in size and coalesce to form large ragged ulcers. They can heal but generally leave scarring [10].

Figure 1. Oral ulcer in a male patient with Behçet's disease.



Note the rolled borders and grayish-yellow necrotic base.

Genital ulcers

GUs are similar in appearance and course to OUs, however, they may not recur as often and can have a scarring tendency. They are usually deeper than OUs and their appearance can be preceded by a tender nodule. They are usually painful or occasionally, asymptomatic, especially in female patients [22,23]. The scrotum is the most frequently involved site in males (**Figure 2**) and the labia in females.

Both OUs and GUs may effect the patients' quality of life. OUs can cause considerable pain and may result in difficulty when eating, drinking, speaking, swallowing and performing routine oral hygiene. GUs may cause severe pain, difficulty with micturition, dyspareunia and marked difficulty in physical activity. Deep ulcers may scar and those in the vagina may be complicated by bladder or urethral fistulae. Vulval ulcerations occasionally lead to labial destruction [3,10].

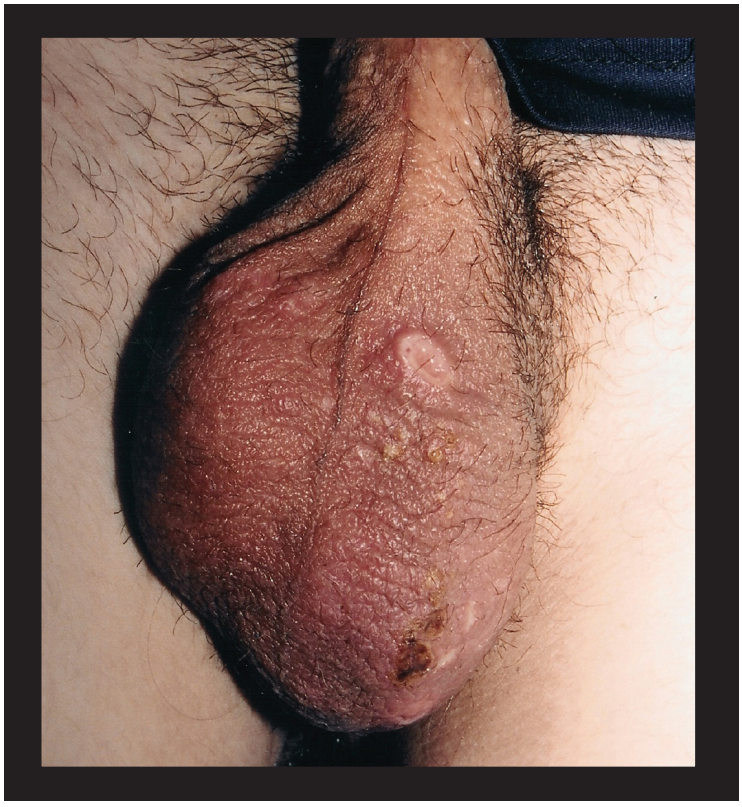
Cutaneous lesions

Cutaneous lesions of the disease vary and mainly include erythema nodosum-like lesions, papulopustular lesions (PPLs), superficial thrombophlebitis, extragenital ulcers, reactivity of the skin to needle prick or injection (pathergy reaction) and other cutaneous vasculitic lesions [10].

Papulopustular lesions

PPLs, the most common type of skin lesions in BD (28–96%), are cutaneous, sterile, folliculitis or acne-like lesions on an erythematous base which appear as a papule and in the course of 24 to 48 h become pustule [24,25]. The trunk and lower limbs are the most common locations [24].

Figure 2. Multiple genital ulcers of the scrotum.



Same patient as in Figure 1. The genital ulcers are similar in appearance to oral ulcers; however, they are deeper than their oral counterparts.

Erythema nodosum-like lesions

Erythema nodosum-like lesions of BD are mostly seen in females and occur in approximately a third of all patients. They have a typical clinical presentation with bilateral, pretibial, painful and hot erythematous nodules. Erythema nodosum-like lesions, can be localized to the face, neck and buttocks. The lesions do not ulcerate and resolve spontaneously within 2 to 3 weeks in pigmented ethnic groups with residual pigmentation; however, recurrence is common [10,26].

Superficial thrombophlebitis

Superficial thrombophlebitis is frequently confused with erythema nodosum-like lesions. Patients usually present with erythematous, tender subcutaneous nodules arranged in a linear fashion. The subcutaneous venules of the extremities, especially in male patients, tend to develop thrombosis leading to sclerosis. The small vein can be palpated as a string-like hardening of the subcutaneous tissue with reddening of the overlying skin. The location of nodules shows a tendency to change from day to day as multiple segments of the vein might be involved, resembling migrating obliterative thrombophlebitis [10,27].

Extragenital ulcers

Extragenital ulcers are relatively common cutaneous lesions and clinically resemble other aphthous lesions of the disease. They are recurrent and usually heal with scarring. In our series, the frequency of this lesion is approximately 6%. The lesions can be seen on various locations such as the legs, axillae, breast, interdigital skin of the foot, inguinal region and neck. Extragenital ulcerations are among the most characteristic and specific findings of the disease and are rarely observed in other skin diseases [10].

The skin pathergy test

The skin pathergy test is a nonspecific skin hyper-reactivity, induced by needle prick or intracutaneous injection. It is associated with a papule or pustule on an erythematous base, similar to the spontaneously occurring PPL of BD. The test positivity is defined as at least one papule observed at the needle-prick site 48 h after application of a sterile needle that penetrated to the corium of an avascular site on the forearm. Test positivity varies between geographic areas (6–71%), and has been reported to be high especially in Japan and the Mediterranean Sea countries [28]. Approximately 60 to 70% of patients with BD in these regions are said to evidence skin hypersensitivity to needle prick. However, the test positivity is uncommon in individuals living in Western countries, which reduces its diagnostic value in these areas. The pathergy reaction is more strongly positive in males [25,29].

Ocular disease

Ocular involvement is a serious complication of BD. It is reported in 30 to 70% of patients [9,30] and is characterized by repeated, explosive ocular inflammatory attacks that may lead to blindness in up to 25% of patients [23]. Ocular symptoms vary from a gritty sensation and blurring of vision, to severe pain and blindness. Anterior uveitis is the most frequent ocular lesion in BD. Panuveitis, posterior uveitis and retinal vasculitis are the other main ocular manifestations. Iridocyclitis, scleritis, keratitis, optic neuritis and retinal vein occlusion may also occur. These are bilateral in most patients. Young male patients are at increased risk for

severe complications of ocular involvement and they usually require aggressive treatment with immunosuppressive agents [30].

Articular disease

Articular involvement is observed in approximately half of the patients. Often nonerosive and nondeforming arthritis with a monoarticular pattern are observed, although asymmetrical polyarthritis can occur. The knee is the most frequently affected joint, followed by the ankle, wrist and elbow. Articular involvement is usually transient in nature with episodes lasting from a few days to weeks [2].

Vascular disease

The disease is a systemic vasculitis affecting arteries and veins of various sizes. The prevalence of vascular involvement in BD has currently been reported at between 7.7 and 60%, in different patient populations. Koc and colleagues have shown that the venous system is the major effected site (88%) and subcutaneous thrombophlebitis is indeed the most frequent type of venous involvement (47.3%) [27]. Thromboses of the superior and inferior vena cava, dural sinuses and Budd–Chiairi syndrome can also be seen and are associated with poor prognosis. Arterial aneurysms and occlusions are relatively rare; however, they are an important cause of mortality. Pulmonary arterial aneurysms have been reported in 1% of a large Turkish cohort [31]. Vascular involvement, particularly arterial disease, can be the presenting feature of BD. Some cases can be diagnosed during a phase of massive hemoptysis or after hemoptysis [32,33].

There is considerable variation in the frequency of cardiac involvement. Pericarditis, coronary valve lesions, intracardiac thrombosis and endomyocardial fibrosis have been observed in patients with BD.

Neurologic involvement

Neurologic involvement is relatively rare; however, it is one of the most serious complication of the disease due to its grave prognosis. The frequency of neurologic manifestations is 5 to 10% [30]. It is more common in males. Parenchymal involvement, including brainstem involvement, hemispheric manifestations, spinal cord lesions and meningoencephalitis is observed in 81% of patients with neurologic involvement. Nonparenchymal involvement, including dural sinus thrombosis, arterial occlusion and/or aneurysms, are relatively rare [34].

Gastrointestinal involvement

GI involvement is characterized by aphthous-like mucosal ulcers occuring predominantly in the iliocecal region, although it can occur throughout the GI tract. It may cause dysphagia, abdominal pain, diarrhea and intestinal perforation. There is considerable geographic variation in the frequency of GI involvement. It is most common in patients with BD from Japan and least common in those from Turkey [30].

Renal involvement, epididymoorchitis and constitutional symptoms such as fatigue, malaise, fever and weight loss, can also occur during the course of BD.

Diagnosis

Due to the lack of a universally recognized pathognomonic laboratory test the diagnosis of BD is primarily based on clinical criteria following the exclusion of an alternative diagnosis. Various criteria have been used and most of them rely heavily on mucocutaneous manifestations, in particular OUs, GUs, cutaneous vasculitic lesions and the skin pathergy test. The International Study Group for Behçet's Disease developed new diagnostic criteria in 1990 which depend on the presence of recurrent OUs, relapsing at least three times over a 12-month period, plus any two of recurrent GUs, typical eye or cutaneous lesions, or a positive skin pathergy test [35].

BD runs a chronic course with unpredictable exacerbations and remissions. Clinical manifestations of BD, with the exception of eye symptoms, tend to improve with time [8,36]. Serious complications such as CNS involvement and sight-threatening eye disease are rarely observed at late onset, especially in cases of onset at 40 years of age or more [37]. Recent studies suggest that besides considerable morbidity, the disease confers an increased mortality, mainly due to the CNS, pulmonary and large vessel involvement as well as bowel perforation [38]. There is evidence that increased morbidity and lethal outcome is often due to delayed diagnosis and treatment. In a previous study, we have shown that the duration between the onset sign and the fulfillment of diagnostic criteria was 3.77 ± 4.43 years [21]. Conversely, the duration between the time point of fulfillment of diagnostic criteria and the diagnosis was around 3 years (2.83 ± 2.3 years). Yazici and colleagues, in their 2-year, randomized, placebo-controlled and double-blind study, reported that in patients enrolled in the study without eye

involvement, azathioprine was significantly better than placebo in preventing the development of eye disease [39]. Therefore, early treatment, to some extent, may control and perhaps change the course of the disease.

Treatment

In general, no therapeutic agent results in the cure of the disease. The choice of treatment is generally based on clinical presentation and the site affected. However, the main aim of the treatment should be the prevention of irreversible organ damage, especially during the early, active phase of the disease. It is wise to remember that male patients and those with early onset disease are associated with more severe presentations including major vessel disease, ocular, GI and neurologic involvement, and therefore require more aggressive treatment. No standard therapy has yet been established for the treatment of BD and a wide spectrum of therapeutic agents have been used, with varying success.

The following sections aim to detail current knowledge regarding the therapeutic approaches including local and systemic agents for the treatment of BD. **Table 1** summarizes the main therapeutic agents used in the treatment of BD.

Topical treatment

The majority of experience in the treatment of OUs comes from studies performed in patients with recurrent apthous stomatitis (RAS). As mentioned previously, OUs of BD are identical to RAS in appearance. Therefore, therapeutic remedies related to RAS can, to some extent, be applied to OUs of BD. It is wise to remember that topical treatment only has a local effect and should almost always be associated with systemic therapy.

Table 1. Effectiveness of therapeutic agents used in the treatment of Behçet's disease.

Theurapetic agent	Comment	Ref.
Topical treatment		
Corticosteroids	Reduce pain severity and accelerates the healing duration of OUs and GUs	[3,22,40–42]
Tetracycline	Decreases pain severity and healing duration of OUs	[42]
Sucralfate	Decreases frequency, healing time and pain of OUs and GUs	[44]
Amlexanox	Decreases pain severity and healing duration of OUs	[47,48]
Anti-inflammatory agents, anesthetics, silver nitrate	Decreases pain severity of OUs	[11,41,49]
Colony-stimulating factor	Decreases pain severity and healing duration of OUs and GUs	[50,51]
Wet dressing	Decreases pain severity and healing duration of EN and Tfb	[3]
Systemic treatment		
Corticosteroids	Effective for mucocutaneous lesions (OUs, GUs, Tfb, ExU), acute uveitis and neurologic disease	[3]
Colchicine	Reduces the occurrence of GUs, EN and arthritis in women, and the occurrence of arthritis in men	[56]
Dapsone	Found to be effective on mucocutaneous lesions (OUs, GUs, EN, PPL), artritis and epididymitis	[59]
Levamisole	Effective in OUs, GUs, arthritis and uveitis	[60]
Interferon-α	Effective choice for mucocutaneous lesions (OUs, GUs, PPL, Tfb), articular and ocular symptoms	[74,75,81]
Thalidomide	Have been found effective in mucocutaneous lesions (OUs, GUs and PPL)	[65]
Azathioprine	Effective in mucocutaneous lesions (OUs, GUs and Tfb), ocular disease and arthritis	[39]
Cyclosporin A	Found to be effective in mucocutaneous lesions (OUs, GUs, PPL, Tfb and EN), ocular, articular and neurologic involvement	[72,73]
Methotrexate	An effective choice for mucocutaneous lesions (OUs, GUs and PPL) and neurologic involvement	[66]
Anti-TNF-α	Effective in mucocutaneous lesions (OUs, GUs, PPL, EN), arthritis, gastrointestinal and ocular disease	[89–91]

EN: Erythema nodosum-like lesions; ExU: Extragenital ulcerations; GUs: Genital ulcers; OUs: Oral ulcers; PPL: Papulopustular lesions; Tfb: Thrombophlebitis; TNF: Tumor necrosis factor.

Although controlled studies are still lacking, the efficacy of topical corticosteroids is indisputable, based on their favorable and widespread use. Topical corticosteroids suppress the inflammation associated with the formation of aphthae, and they are effective for both OUs and GUs, especially when used in the early stage of these lesions [3]. They reduce pain severity and accelerate the healing duration of OUs and GUs. Triamcinolone acetonide as a cream 0.1% in orabase or spray, prednisolone tablets in 20 ml water as a rinse four-times daily (i.e., 0.5 mg/5 ml of dexamethasone elixir) can be used for OUs. Potent corticosteroid creams alone or in conjunction with antibiotics are also effective in GUs [22,40]. The same combination can also be used for extragenital ulcers and PPL. Major OUs or GUs can be treated by intralesional triamcinolone, 5 to 10 mg/ml [22,41,42]. Topically applied corticosteroid eye drops may also be used in mild attacks of anterior and intermediate uveitis together with mydriatics or cycloplegic agents [3,43]. Antimicrobial agents including antibiotics and antiseptic agents are used to control microbial contamination and secondary infection. Antiseptic agents (hexetidine, chlorhexidine and listerine) reduce pain in OUs [3]. Antibiotics, especially tetracycline, have been widely used in RAS and OUs of BD for years [42]. Tetracycline mouthwash (250 mg capsules dissolved in 5 ml of water or flavored syrup and held in the mouth for approximately 2 min before swallowing, four-times daily) decreases the pain severity and duration of OUs. Sucralfate (1 g/5 ml), four-times daily, for a 3-month duration as mouthwash, significantly decreases the frequency, healing time and pain of OUs and GUs. The effectiveness of sucralfate on OU frequency and healing time continues during the post-treatment period in decreasing order [44]. This compound binds to ulcerated tissue and forms a barrier augmenting ulcer healing [45,46]. Amlexanox accelerates the healing and decreases the pain severity of ulcers in RAS [47,48]. Amlexanox is used as in an oral paste (5%) four-times daily (after meals and at bedtime) for 4 to 10 days. Anti-inflammatory agents (benzydamine, diclofenac), anesthetics (lidocaine 2–5%, mepivacaine 1.5%, tetracaine 0.5–1% gels or mucosal ointments) and silver nitrate, in general, reduce the pain severity of aphthous lesions [10,41,49]. Beneficial effects of colony-stimulating factor on the healing duration and pain severity of OUs and GUs have also been reported [50,51].

In addition to the above-mentioned treatment approaches to OUs, patients should be advised to maintain good daily oral hygiene. These patients should avoid irritating agents such as acid, crusty, hard, spicy or salty foods and alcoholic beverages. Erythema nodosum-like lesions are treated topically similar to those of classic erythema nodosum. Wet dressings, such as aluminum acetate 3 to 5% (Burow's solution),can be applied for 10 to 20 min and repeated during the day for 3 to 5 days in the early stage of erythema nodosum-like lesions. This approach is also helpful for the treatment of thrombophlebitis. All therapies should be combined with rest in bed [3].

Systemic treatment

Corticosteroids

Corticosteroids have been widely used for almost all lesions of the disease. The compound is an effective choice especially in mucocutaneous lesions, acute uveitis and neurologic disease. They can be given as monotherapy or in combination with other drugs such as colchicine, interferon (IFN)-α, cyclosporine or azathioprine. However, in a recent randomized, placebo-controlled study of 86 patients who had active mucocutaneous lesions without eye and major organ involvement, low-dose depot steroid (40 mg of methylprednisolone acetate every 3 weeks) was only found to be helpful in controlling erythema nodosum-like lesions, especially among females [52]. Conversely, the well-known side-effect profile of corticosteroids in higher doses limits their long-term use. Corticosteroids do not improve the long-term outcome in BD. We recommend prednisolon 40 to 60 mg/day for 1 to 2 weeks and then taper the dose gradually over 4 weeks.

Colchicine

Colchicine inhibits the enhanced chemotactic activity of neutrophils [53]. Promising results with colchicine (0.5–2 mg/day per oral) have been reported, especially after 1975 [54]. However, first placebo-controlled study suggested that the drug is only effective for erythema nodosum-like lesions and arthralgia [55]. Yurdakul and colleagues, in a recent randomized, double-blind and placebo-controlled study, revisited the issue and have shown that colchicine reduces the occurrence of GUs, erythema nodosum-like lesions and arthritis among women, and the occurrence of arthritis among men [56]. Oligozo-ospermia, amenorrhea or dysmenorrhea, malaise, hair loss, GI complaints (nausea, vomiting and diarrhea) and hematologic side effects are the main adverse effects of colchicine.

Calguneri and colleagues have found the combined use of colchicine and benzatin penicillin 1.2 MU/3 weeks to be more superior than colchicine alone [57]. The combined treatment was effective in reducing frequency and duration of OUs and erythema nodosum-like lesions and the frequency of GUs.

Dapsone

Dapsone (100–150 mg/day per oral) also inhibits the enhanced chemotactic activity of neutrophils and can be used as an alternative compound to colchicine. Although quick relapses have been observed after discontinuation of the treatment, the beneficial effects of dapson have been reported [58]. In a double-blind, placebo-controlled study of 20 patients, Sharquie and colleagues reported significant reductions in the OU and GU parameters as well as the incidence of cutaneous manifestations (erythema nodosum-like lesions and PPL) in dapsone-treated patients [59]. The treatment was also found to be effective on arthritis and epididymitis. Hemolytic anemia and methemoglobulinemia, which can be severe in patients with glucose-6-phosphate dehydrogenase deficiency, are the main side effects and may significantly limit their use.

Levamisole

Levamisole is an antihelmintic agent and is used widely both in RAS and BD patients for years due to its immunopotentiating effects. Lehner and colleagues evaluated the efficacy of levamisole in a double-blind, crossover study, and reported an improvement in OUs and GUs together with arthritis and uveitis [60]. In an open study, De Merieux and colleagues reported that levamisole is effective in OUs, GUs and ocular inflammation [61]. Hamza and colleagues in 1982 [62] and Lavery and colleagues in 1985 [63], reported similar beneficial effects. However, there haven't been publications on these treatments more recently, probably as the compound was not found to be effective enough and newer, more effective treatments have appeared during the last two decades. Taste disturbances and nausea are the major adverse effects of levamisole. Neutropenia, flu-like symptoms, skin rash and urticaria have also been reported.

Thalidomide

Thalidomide has been approved for the treatment of male and sterilized as well as postmenopausal women with BD in the USA [64]. The drug selectively inhibits TNF-α synthesis. In a randomized, double-blind, placebo-controlled study with 63 patients, a remission of OUs and GUs and PPL was detected in 22% of the patients over 8 weeks [65]. During the 6-month treatment 30% of the patients remained free of lesions. However, the effect of thalidomide is temporary, and discontinuation of the treatment results in recurrence of OUs and GUs, therefore a maintenance treatment with 50 mg/day to 50 mg twice a week is required. Peripheral neuropathy with acral paresthesia was found clinically in 6% and electrophysiologically in 22% of the patients who received thalidomide 100 to 300 mg/day over 6 months. Thalidomide therapy however, was associated with exacerbation of erythema nodosum. CNS signs with sleepiness and headaches as well as xerostomia and constipation can occur. Teratogenic risk of thalidomide limits the clinical application. The effectiveness of the thalidomide is lost about 20 days after discontinuation of the drug.

Azathioprine

Azathioprine, an important disease-modifying compound, shows an anti-inflammatory effect by suppressing both cellular and humoral immune responses. In a randomized, double-blind and placebo-controlled study of 73 patients, azathioprine (2.5 mg/kg body weight/day per oral) was found to be an effective choice in OUs, GUs and thrombophlebitis besides ocular inflammation and arthritis [39]. The treatment resulted in a decrease in the frequency of OUs, GUs and thrombophlebitis. Azathioprine was found to be significantly better than placebo in preventing the development of new eye disease. Therefore, the authors concluded that the drug can by used profilactically to prevent the eye involvement in young, male patients presenting with severe mucocutaneous lesions. Sterility, myelotoxicity, immunosuppression, opportunistic infections and liver disease are the main side effects.

Methotrexate

Methotrexate (7.5–20 mg once a week per oral over 4 weeks) has been reported to induce improvement of severe mucocutaneous involvement as well as neurologic involvement [66]. Methotrexate is not recommended in pregnancy and lactation, and severe bone marrow depression, liver dysfunction, acute infections, renal insufficiency and mucositis are important side effects of the drug.

Chlorambucil

Chlorambucil is a slow-acting alkylating agent which causes crosslinking of DNA resulting in altered protein production, decreased cell division and cell death. Uveitis and meningoencephalitis are the major indications of this compound in patients with BD. It has been found to be more effective when the drug is combined with corticosteroids [67,68]. In a comparative study, Pivetti and colleagues, reported that cyclosporin A (CyA) and chlorambucil are equally effective therapies [69]. Chlorambucil therapy resulted in long-lasting activity, whereas, cyclosporin therapy caused remission in a shorter time period. The usual starting dose is 0.1 mg/kg and the maintenance dose, 2 mg/day. Toxicity of the drug limits its usage in BD. Myelosuppression, infection, infertility and secondary malignancy are the main side effects.

Cyclophosphamide

Cyclophosphamide is a fast-acting alkylating agent. It has been found to be a beneficial therapeutic agent for eye disease and systemic vasculitis (neurologic involvement and arterial aneurysms) [70,71]. In a a double-blind crossover study, it was shown that the combination of cyclophosphamide and corticosteroid therapy is superior to corticosteroid therapy alone in eye involvement [70]. It is used at a dose of 2 to 3 mg/kg/day or 750 to 1000 mg/m^2/day as pulse treatment. Myelosuppression, pulmonary fibrosis, renal toxicity, hemorrhagic cystitis, infertility, malignancy and alopecia are the major adverse effects of cyclophosphamide.

Due to the severe toxicity, alkylating agents (chlorambucil and cyclophosphamide) should be selected in cases with clinically significant disease that are refractory to other agents.

Cyclosporin A

CyA is an immunosuppressive agent which selectively inhibits T-lymphocytes. There have been several reports of the effectiveness of CyA. The drug is capable of markedly ameliorating uveitis as well as mucocutaneous lesions. CyA is still the most effective agent for the treatment of uveitis which reduces the frequency of ocular exacerbations and improves visual acuity. In a controlled study of 96 patients with recurrent uveitis, CyA (10 mg/kg/day) has been shown to be superior to colchicine (1 mg/day) in decreasing frequency and severity of ocular attacks [72]. CyA is also found to be effective for mucocutaneous lesions; however, it should be reserved for the most severe cases due to its significant long-term adverse effects such as renal failure, hypertension, neurologic toxicity and hirsutism. In another controlled trial, 26 patients treated with CyA with a dose of 5 mg/kg/day were compared with 50 patients receiving conventional therapy, systemic corticosteroid alone or combined with azathiopurine [73]. CyA treatment was found to be more effective in reducing OUs, GUs, cutaneous lesions and thrombophlebitis as well as articular and neurologic symptoms.

Interferon

In recent years, increasing evidence has suggested that IFN-α is an effective alternative in the treatment of BD; however, the mode of action is still unknown. However, their antiviral and immunomodulatory effects appear to be possible mechanisms. The putative association between BD and viral infection, particularly herpes simplex virus 1, has been suggested to explain their therapeutic potential in BD. Regarding the immunomodulatory effects of IFN-α; enhancement of human leukocyte antigen (HLA) class I expression on lymphoid cells, enhancement T and natural killer (NK)-cell cytotoxicity and diversion of the T-cell response in the direction of Th1 has been suggested as an explaination for the mechanism of action of IFN in BD. Inhibition of the proliferation of γ and δ T-cells, which are increased in BD may also have a role [74,75]. Promising results have been reported especially with IFN-α2a [76–79]. A majority of patients showed a worthwhile improvement in mucocutaneous lesions, arthritis and ocular manifestations. A 2-month treatment schedule, at least, is likely to be necessary to increase the effectiveness, and the disease generally relapses upon discontinuation [80]. In a recent randomized, double-blind, placebo-controlled study, this authors' group showed that IFN-α2a treatment with a dose of 6 MU, three times a week, for 3 months is an effective alternative, particularly for the management of mucocutaneous lesions of BD, and its effect decreases gradually after the cessation of treatment [74]. IFN-2a treatment decreased significantly the duration and pain of OUs, and the frequency of GUs and PPL. The mean frequency and duration of erythema nodosum-like lesions, thrombophlebitis and articular symptoms also showed a decrease. Recently, IFN-α has been employed in cases of sight-threatening refractory uveitis in BD with promising results. Kötter and colleagues in their

open-label, prospective study, used IFN-2a in 50 patients at a dose of 6 MU daily, tapered according to a preset schedule [81]. After a mean observation period of 36.4 months, 20 patients (40%) were off treatment and disease-free for a mean period of 30 months. In the other patients, IFN was maintained at a dose of 3 MU, three times a week. The response rate of the ocular manifestations was found to be 92%. The authors concluded that IFN-2a is effective in ocular BD, leading to significant improvement of vision and complete remission of ocular vasculitis in the majority of patients. A recent, open-label study by Calguneri and colleagues, evaluated the IFN treatment in patients with ocular, articular, vascular or neurologic manifestations [82]. They treated 29 patients who were resistant to conventional treatments. The overall response rate was 96%. IFN-α therapy produced a remission in all patients with vascular and neurologic disease, and moreover, no recurrence or major toxicity was observed during the follow-up.

The primary side effects of IFN-α therapy include flu-like symptoms (fever, chills, headache, fatigue and myalgia) that start a few hours after the initiation of therapy and continue for less than a day. Nausea, vomiting, anorexia, diarrhea, loss of weight, hematologic changes and transient raising of hepatic transaminases are observed less frequently [74,75].

Antitumor necrosis factor-α

Two anti-TNF-α compounds have shown favorable results in preliminary tests of infliximab and etanercept. Infliximab is an antibody that neutralizes the biologic activity of TNF by binding with high affinity to the soluble and transmembrane forms of TNF. Recent trials of infliximab for BD have shown encouraging results in the treatment of GI [83] and ocular symptoms [84,85], arthritis [83] and cerebral vasculitis [86] besides recalcitrant mucocutaneous lesions, namely OUs, GUs and erythema nodosum-like lesions [87,88]. In a recent study, Sifitakis and colleagues used a single infusion of infliximab (5 mg/kg) to 25 patients with relapsing panuveitis, at the immediate onset of last relapse [89]. Remission of acute ocular inflammation was evident within the first 24 h in 24 of 25 patients and complete suppression of vitritis and retinitis was seen at day 28 after treatment in all patients. Retinal vasculitis and cystoid macular edema, the most resistant manifestation, resolved in 94 and 90% of patients by day 28, respectively. The authors concluded that infliximab treatment should be considered at the onset of a sight-threatening relapse due to the rapid control of ocular inflamation of this compound. In another study, Ohno and colleagues showed that infliximab treatment (repeated four times at a dose of 5–10 mg/kg) decreases the frequency of ocular attacks dramatically in patients with refractory uveoretinitis [90].

Etanercept is a dimeric fusion protein of the p75 kd TNF-α receptor and Fc portion of human immunoglobulin (Ig)G_1. In a recent double-blind, placebo-controlled study of 40 male patients with BD, etanercept (25 mg twice a week, subcutaneously) has been reported to be beneficial in decreasing the number of OUs, erythema nodosum-like lesions and PPL as well as arthritis episodes [91]. However, recurrences developed in some patients 3 months after etanercept therapy was stopped.

However, there are still important questions to be answered for anti-TNF-α agents; optimal dosage, frequency of infusion and the long-term consequences and side effects. Therefore, it is suggested that these compounds should be considered only if conventional modes of treatment are not successful in suppressing the distressing aspects of the condition.

Adverse effects of anti-TNF agents include infection (sinusitis, pharyngitis, bronchitis and urinary tract infections and reactivation of tuberculosis), autoimmune reactions (e.g., lupus-like syndrome), lymphoproliferative disorders, delayed hypersensitivity reactions and neurologic, cardiac and GI symptoms.

Autologous hematopoietic stem cell transplantation

Rossi and colleagues have recently reported the successful treatment of a child with severe/refractory intestinal BD, by lymphocyte-depleted autologous hematopoietic stem cell transplantation following high-dose immunosuppressive therapy [92].

Surgical treatment

Although various treatment modalities appear, surgical intervention is often indicated for arterial aneurysms. In patients with recurrent or massive hemoptysis, surgery may be necessary. Endovascular treatment for pseudoaneurysms due to BD seems to be an effective choice when disease activity is strictly controlled with immunosuppressive therapy [32,33]. In other serious consequences, such as GI bowel perforation, enterocutaneous fistula formation, thrombotic

obstruction in large-caliber vessels and cardiac involvement, surgery may also be the only possible treatment option.

Expert commentary

Treatment of BD has become much more effective in recent years. Due to recent advances in understanding the pathogenesis of the underlying disease and availability of a wide spectrum of therapeutic agents, alleviation of most symptoms, control of the disease or even, modification of the course of the disease, are now possible.

Mucocutaneous manifestations alone, especially in those who do not have severe organ involvement such as ocular or neurologic involvements and large vessel disease, do not warrant the use of immunosuppressive agents. Topical treatments should be the first stage for these patients. However, patients with severe mucocutaneous disease or those who are unresponsive to topical treatments, require systemic approaches to control their disease such as corticosteroids, colchicine, dapson, IFN or azathioprine. Systemic treatment should also be given for those ulcers developed in the oropharynx, a location resistant to topical treatment, and for major ulcers that frequently do not respond to topical treatments. Systemic treatment should also be considered for young male patients presenting with severe mucocutaneous lesions, to prevent the development of serious organ involvement. In ocular disease, immunosuppressives, such as cyclosporine and azathioprine, can be used effectively. Recent studies have confirmed that IFN-α is an effective choice for the treatment of ocular disease. Although several promising therapies are evolving, the treatment of severe disease (large vessel and neurologic involvements) is not entirely satisfactory, and the treatment of those remains predominantly empiric. In recent years, numerous case reports and studies have reported the efficacy of anti-TNF treatment in cases resistant to conventional therapy, particularly to immunosuppressors. Therefore, biologics, especially IFN-α and infliximab, seem to be effective newer treatments in BD and may have the potential to improve survival and prognosis. However, the high cost, need for injections, troublesome toxic side effects and the inability to cure the disease, are the limitations for widespread acceptance of these compounds as a first-line choice for the management of BD. There still remains a need for further controlled, double-blind studies in a large series.

Outlook

In conclusion, as a high incidence of vital organ involvement, as well as increased mortality especially in young male patients, has been recorded in patients with BD, continuous surveillance and good management of the disease is warranted. In this respect, patient-based organizations that are now allied with cognizant physicians should be encouraged.

Highlights

- Relapsing bipolar oral and gential ulcers are strongly evocative of Behçet's disease.
- Besides considerable morbidity, Behçet's disease confers an increased mortality, mainly due to CNS, pulmonary and large vessel involvement, as well as bowel perforation.
- Biologicals, especially interferon-α and infliximab, appear to be effective newer treatments in Behçet's disease, and may have the potential to improve patient prognosis and survival.

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