Behçet’s syndrome: Facts and controversies

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Abstract Behçet’s syndrome is a systemic vasculitis of small and large vessels affecting both veins and arteries. Almost all patients with Behçet’s syndrome have recurrent oral aphthae, followed by genital ulcers, variable skin lesions, such as erythema nodosum and papulopustular lesions, arthritis, uveitis, thrombophlebitis, and gastrointestinal and central nervous system involvement. Recent epidemiologic works suggest that genetic factors are more important than environmental factors in its pathogenesis. European League Against Rheumatism guidelines were recently published for the treatment of Behçet’s syndrome. Although these are quite useful for the management of mucocutaneous, eye, and joint involvement, treatment of vascular, neurological, and gastrointestinal involvement are still problematic as there are no controlled studies for these manifestations. This contribution addresses the epidemiology, mucocutaneous manifestations, diagnostic criteria, and evidence-based therapies, including biologic agents.

Introduction

Hulusi Behçet, a Turkish dermatologist from Istanbul, described three patients with recurrent oral and genital ulceration, hypopyon uveitis, and erythema nodosum in 1937. The following observations showed that musculoskeletal, neurologic, vascular, and gastrointestinal (GI) involvement also might be part of the spectrum. Almost all patients with Behçet’s syndrome have recurrent oral aphthae, followed in decreasing frequency by genital ulcers, erythema nodosum and papulopustular lesions, arthritis, uveitis, thrombophlebitis, and GI and central nervous system involvement. The etiology of Behçet’s syndrome is unknown. The disease is a systemic vasculitis of small and large vessels affecting both veins and arteries. The underlying pathology shows a nonspecific inflammatory process of blood vessels.

In this contribution, we review some aspects of Behçet’s syndrome focusing on epidemiology, mucocutaneous manifestations, diagnostic criteria, and therapeutic approaches including the biologic agents.

Epidemiology

The usual onset of Behçet’s syndrome is in the third decade. The disease is rare in individuals older than age 50 years and during childhood. Although both sexes are equally affected, the syndrome runs a more severe course among young men (ages <25).

Behçet’s syndrome is more frequent in the countries along the “Silk Road,” an ancient trading route, where the
prevalence of HLA-B5(51) also is relatively high compared with the other parts of the globe. The five cross-sectional field surveys conducted in different regions in Turkey showed a prevalence of Behçet’s syndrome between 20 and 421 among 100,000 adult individuals. The age of the screened population was older than 10 years. This was lower in European countries, being 20 and 80 compared with 110, 370, and 431, respectively, on the Asian side. Other population-based surveys gave similar figures with a rate of 17 in Iraq, 20 in Saudi Arabia, and 80 in Iran. Although one hospital-based study estimated a prevalence of 120 per 100,000 in an Arab community in Israel, another one in the same country gave a rate of 8.6 for Jews, 26 for Arabs, and 146 for Druzes. The prevalence in Japan, based on hospital records was 13.5 per 100,000 individuals.

Based on case registries and hospital records, the estimated prevalence rates are variable in Europe: 0.64 for the United Kingdom, 1.2 for Sweden, 1.5 for Portugal, 3.7 for Italy, and 5.6 to 7.5 per 100,000 for Spain. The prevalence was low for Germans as expected (1.47 per 100,000), whereas it was significantly higher, among immigrant Turks living in Berlin, Germany (77 per 100,000), indicating a genetic load. This rate for Turks in Germany, however, is lower compared with 110, 370, and 431 in Asian Turkey, suggesting an environmental role. A recent cross-sectional prevalence study in the suburbs of Paris showed that the frequency of Behçet’s syndrome was 7.1 per 100,000. As expected, it was 2.4 for Europeans, 17.5 for Asians, and 35 per 100,000 in North Africans living in Paris. The same study group also found a combined rate of 9 per 100,000 for all the frequencies of vasculitis including polyarteritis nodosa, microscopic polyangiitis, Wegener’s granulomatosis, and Churg–Strauss syndrome, similar to Behçet’s syndrome. A recent study also showed ethnic variations of disease prevalence in Istanbul, Turkey. According to this study, ethnic Armenians living in Istanbul have a lower frequency of Behçet’s syndrome (110 per 100,000), whereas the general population has a fourfold increased frequency (420 per 100,000).

In 1975, a survey of postal questionnaires showed that there were no patients with Behçet’s syndrome in Hawaii, where 217,307 Japanese, a genetically susceptible population, lived. Later, an estimated rate of 5.2 per 100,000 individuals was reported in Olmsted County, Rochester, Minnesota. There are only few case reports from the rest of the globe.

**Mucocutaneous lesions**

**Recurrent aphthous stomatitis**

One of the most common signs of Behçet’s syndrome is recurrent aphthous stomatitis, which has a frequency of 97% to 100%. It is usually the initial sign of the disease and the syndrome is usually diagnosed 6 to 7 years after the first attacks of aphthous stomatitis. This data, however, depends on retrospective patient series.

The aphthae, which can be observed on any nonkeratinized mucosal membrane surfaces in the oral cavity, usually start as painful papules and rapidly become ulcerated. They are mostly found in buccal mucosa and the lateral and ventral surfaces of the tongue. The surfaces of the aphthae are covered with white to yellowish pseudomembranes, surrounded by an erythematous halo (Figure 1). Lesions with a diameter less than 10 mm are named as minor aphthae. These usually heal within 7 to 10 days, without any scar formation. Major aphthae are painful ulcers, with a diameter more than 10 mm, and they may heal with scarring. Herpetiform aphthae are characterized by the coalescence of multiple ulcers. The drug trials performed by the Cerrahpasa Behçet group showed that minor aphthae are the most commonly seen type, whereas major and herpetiform types are very rare. In one study, major aphthae were more frequently observed among women. For recurrent aphthous stomatitis, there was no relation between gender and types of aphthae.

According to the International Study Group (ISG) for Behçet’s Syndrome diagnostic criteria, aphthae must recur more than three times a year for diagnosis of Behçet’s syndrome. Recurrent aphthous stomatitis also is seen in association with other conditions such as inflammatory bowel disease (IBD), celiac disease, hematinic deficiencies, systemic lupus erythematosus, reactive arthritis, formerly called Reiter’s syndrome, mouth and genital ulcers with inflamed cartilage syndrome, cyclic neutropenia, and auto-inflammatory diseases (familial Mediterranean fever, periodic fever, aphthous ulcers, pharyngitis, adenopathy, hyperimmunoglobulinemia D).
Incidental trauma such as tooth brushing, gum chewing, or eating foods with sharp and rough textures can trigger the formation of new aphthous lesions in patients with a history of recurrent aphthous stomatitis. In an uncontrolled study, Sharquie et al. performed a pathergy test to the oral mucosa of patients with Behçet’s syndrome. The needle-prick test caused pustule formation on the mucosa in 85% of the patients (33 of 39) and ulcer formation was observed in six of them (15%).

A relationship between smoking and a low frequency of oral aphthae has been shown in Behçet’s syndrome. It has been claimed that some of the symptoms can be activated after the patient stops smoking. Forty-seven asymptomatic current smokers with Behçet’s syndrome stopped smoking and 31 (65.9%) developed oral aphthous ulcers at the end of a 1-week period. Only 15 of 60 (25%) nonsmoking Behçet patients in the control group developed oral aphthous ulcers. In another study, a significant inverse association was found between smoking and the presence of oral aphthous ulcers.

In histopathologic examination, normal squamous cell epithelium is replaced with necrotic fibropurulent exudates. There is dense neutrophil, plasma cell, lymphocyte, and histiocyte infiltration under the mucosal surface. Vascular proliferation and swollen endothelial surface are also cardinal findings. It usually is not possible to differentiate these lesions from recurrent aphthous stomatitis with histologic investigation.

Genital ulcers

One of the cardinal findings of Behçet’s syndrome is genital ulcer. In men, the ulcers are mostly found on the scrotum and inguinal area. Penile lesions are quite rare and urethritis is not observed, in contrast to reactive arthritis. Vulva and femoral-inguinal regions are common locations in women. Ulcers are painful at the initial phase, beginning as papules, pustules, or necrosis. The floor of the ulcer is covered with fibrin layer, with a surrounding edematous swelling (Figure 2). Borders of the ulcers are sharp and punched out. These lesions usually heal within 2 to 4 weeks. The frequency of genital ulcers in Behçet’s syndrome is about 50% to 85%. In a prospective study, we showed that genital ulcers larger than 1 cm in diameter, usually healed with scar formation in men (89%, 59 of 66), whereas small-diameter ulcers caused scarring in only 49% (15 of 37). In women, 60.7% (34 of 56) of ulcers located in major labium and femoral-inguinal regions can cause scar formation; whereas the ones in minor labium and vestibule usually heal without scar tissue. Vaginal and cervical ulcers are rarely observed.

In histologic examination, early neutrophilic infiltration is prominent similar to oral aphthae. In older lesions, lymphocytes, histiocytes, and plasma cells also are seen. Half of the patients have lymphocytic vasculitis, but leukocytoclastic vasculitis is very rare.

Erythema nodosum

Erythema nodosum usually is found in the lower extremities, characterized by red, painful nodules of 1 to 5 cm in diameter. They are observed in about half of the patients with Behçet’s syndrome and usually are located on pretibial surface of the lower extremity, in a symmetrical pattern. Arms, thighs, and hips also can be involved. They are more commonly observed in females, and they heal with pigmentation in 1 to 6 weeks.

They have histologic properties of septal panniculitis. Some cases have histologic features of lobular panniculitis with vasculitis, resembling nodular vasculitis. Vascular inflammation with neutrophilic infiltration is observed in almost all of the cases. In one study, neutrophilic vasculitis was noted in 42% (10 of 24, first observer) and 46% (11 of 24, second observer) of nodular lesions of Behçet’s syndrome. Twenty-nine percent (7 of 24, first observer) and 42% (10 of 24, second observer) of the cases with Behçet’s syndrome demonstrated a lymphocyte-predominating cellular infiltrate. Necrobiosis and leukocytoclasia also are other frequently observed findings. Granuloma formation rarely is seen.

Superficial thrombophlebitis

Superficial thrombophlebitis migrans is another lesion seen in patients with Behçet’s syndrome. They are more
commonly observed in men. The nodules generally are located on the medial side of the tibia, and in the course of the great saphenous vein, where stringlike red nodules occasionally are observed. New lesions appear as the older ones heal with a marked hyperpigmentation. Superficial thrombophlebitis migrans also can be related to deep vein thrombosis. Histopathologic evaluation is the gold standard in its differentiation from erythema nodosum. High-resolution ultrasonography is also a helpful and noninvasive method of differentiation. The main sonographic findings of superficial thrombophlebitis migrans are hypoechoic nodules, presence of thrombus in the lumen of the vein, and negative compression. Hyperechogenicity and regular contours, on the other hand, are distinct features of erythema nodosum.

Papulopustular lesions

Another frequent finding of Behçet’s syndrome are the papulopustular lesions. They are seen in 30% to 96% of the cases. Acneiform lesions are polymorphic in nature, with inflammatory findings like papules or pustules and noninflammatory comedons. These acneiform papules and pustules are found on the back, chest, and shoulder areas and less commonly on the face, which is the preferred location of acne vulgaris. According to the ISG diagnostic criteria, acneiform lesions in postadolescent patients who are not on systemic corticosteroid treatment are interpreted as a sign of Behçet’s syndrome. In studies evaluating the papulopustular lesions of Behçet’s patients, the mean age of the patients is greater than 30 years. Acne vulgaris also can be observed in 20% of men and 35% of women over the age of 30, according to one study. Postadolescent acne persisting beyond the age of 25 years usually is seen in women during the last week of the menstrual cycle. Typical clinical findings are tender, deep-seated papulonodules on the lower third of the face, jaw line, and neck.

It is also worth noting that these papulopustular lesions are more frequent in patients with Behçet’s syndrome with comorbid arthritis, suggesting a reactive form of arthritis in Behçet’s syndrome.

Papulopustular lesions are mostly follicular. Although they once were regarded as noninfectious sterile pustules, the latest studies showed the presence of coagulase-negative *staphylococcus* and *provotella* species in the lesions. In a study with 17 patients with Behçet’s syndrome and 6 with acne vulgaris, histopathologic examinations were made by a blinded dermatopathologist. Fifteen of the patients with Behçet’s syndrome demonstrated a predominant perifollicular infiltrate, whereas two had a perivascular infiltrate. When epidermis, follicle epithelium, and dermis were examined separately, no differences could be found between the two groups. The papulopustular lesions seen in these two disorders could not be distinguished on the basis of clinical and histopathologic findings. In another study, two dermatologists and one pathologist examined 23 papulopustular lesions in 20 patients with Behçet’s syndrome. Of these papulopustular lesions, 13% (3 of 23) showed findings consistent with leukocytoclasic vasculitis.

Other skin lesions

Sweet syndrome can be seen in about 4% of the cases throughout the course of Behçet’s syndrome. These lesions usually are acutely developing painful and erythematous papules and nodules, located mostly on the face and extremities. Aphthous ulcers, uveitis, and arthritis also can be components of Sweet syndrome. Extra-genital ulcers are rather rare, and they are located in the axillary region, inframamillary area, and interdigital area of the feet.

Ulcus cruris (Figure 3) or vasculitic ulcers can be observed in patients with a history of deep vein thrombosis.

Pathergy phenomenon

Another important finding of Behçet’s syndrome is the pathergy phenomenon. The test is applied to the hairless area of forearm skin. After cleaning with alcohol, 20-gauge needles are inserted in a vertical or oblique way through the dermis. Development of papules and pustules after 48 hours, are regarded as positive results (Figure 4). The rate and intensity of pathergy positivity are very high in young, male Behçet patients. It is accepted as one of the diagnostic criteria by the ISG guidelines. The incidence of pathergy...
positivity shows variation among different geographical regions. For instance, the positivity rate is quite low in the United Kingdom, but is approximately 69% in our patient series. The rate of positivity increases if the test is applied with blunt needles, which can cause excessive trauma to the skin. It was reported that there has been a decrease in pathergy positivity after the routine use of disposable needles, but we still use sterile disposable needles in our clinical practice. Surgical cleaning of the forearm also decreases the positivity rate.

Surgical interventions can cause nonspecific and severe inflammatory reactions in Behçet’s syndrome patients with a similar mechanism of pathergy phenomenon. The positivity of pathergy is not similar in each patient when repeated at different times. The intraobserver and interobserver variations of pathergy readings are less than 10% each.

Dermal inflammation occurring as a response to intradermal needle is composed mainly of lymphocytes, neutrophils, and eosinophils around the vessel wall. Biopsy specimens taken from the site of reaction 12 hours after the test show findings compatible with the early phase of inflammation. After 24 hours, the intensity of the inflammatory cell infiltration is prominent. Edema, leukocytoclasia, intradermal pustule formation, and necrosis in some instances also are identified histologic findings. Some authors describe the presence of a mixed inflammatory infiltration. Mononuclear cell infiltration is prominent in the dermis 48 hours after the application of the pathergy test and is mainly composed of CD4+ T cells. Vascular endothelial cells strongly express ICAM-1 and E-selectin in a lesser intensity. VCAM-1, on the other hand, is not expressed. In light of this information, the cause of cutaneous inflammation may be interpreted as epidermal damage.

In patients with Behçet’s syndrome, the pathergy reaction is mediated by T-helper 1 CD4+ cells. The response reaction to the needle is nonspecific, but cytokine release plays a major role in the inflammatory process. Injection of intradermal monosodium urate crystals causes erythema and induration after 48 hours, whereas this reaction cannot be supressed with etanercept.

Uncommon skin lesions

Pyoderma gangrenosum-like lesions, pernio-like lesions, neutrophilic eccrine hidradenitis, and Kaposi’s sarcoma can be seen in the course of the disease.

Eye involvement

Eye involvement is observed in half of the patients as a chronic and relapsing bilateral uveitis involving both anterior and posterior chambers. Isolated anterior uveitis is infrequent but hypopyon uveitis (anterior uveitis with intense inflammation) is seen in 20% of the cases (Figure 5) and signifies a poor prognosis as it is associated with severe retinal disease. The main symptom of anterior uveal tract inflammation is photophobia, whereas that of posterior tract inflammation is visual loss. Posterior uveal inflammation with involvement of the retina can be very severe, causing retinal exudates, hemorrhages, papilloedema, and macular disease. These inflammatory structural changes lead to permanent loss of vision if urgent anti-inflammatory therapy is not initiated.

Musculoskeletal involvement

One year after the original description of the disease, Behçet himself mentioned “rheumatoid pains” in 1938 and then myositis, associated with the acute exacerbation of the disease. Joint involvement is seen in half of the patients as either arthritis or arthralgia. The arthritis is usually monoarthritis or oligoarthritis (two to four joints) during an attack. Peripheral arthritis is not deforming and resolves in a few weeks. The most commonly involved joints are the knees, followed by ankles, wrists, and elbows. Radiologic erosions are quite rare. Back pain is uncommon, and properly controlled studies of sacroiliac joint involvement have not demonstrated an increased prevalence in Behçet’s syndrome.

Patients with Behçet’s syndrome and arthritis also have more acne lesions. In addition, patients with arthritis and acne have significantly more enthesopathy, suggesting a link with the reactive arthritides. A recent study has shown that the frequency of HLA B-27 and sacroilitis was not
increased in these patients. These studies support the hypothesis that patients with Behçet’s syndrome and arthritis and acne form a distinct cluster and this cluster has recently been shown in familial cases as well.

Synovial fluid is commonly inflammatory, but a good mucin clot is usual. Synovial histology shows a non-diagnostic, non-specific synovitis.

Fibromyalgia can be associated with Behçet’s syndrome, especially among the female patients. Local and generalized myositis is rare in Behçet’s syndrome. Serum muscle enzyme levels may be elevated in some cases. Histologic changes are similar to those of idiopathic polymyositis. Another rare musculoskeletal manifestation of Behçet’s syndrome is aseptic necrosis of the bones.

Vascular and cardiac lesions

Up to one-third of patients have thrombophlebitis of the superficial and/or the deep veins, usually in the leg. Thrombosis of the major veins such as superior or inferior vena cava can occasionally be seen. Occlusion of suprahepatic veins, Budd-Chiari syndrome, is rare but carries a high mortality. Although there is a high frequency of thrombophlebitis in Behçet’s syndrome, thromboembolism rarely is reported, most probably due to firm adherence of thrombi to the diseased veins.

Although arterial involvement is less frequent (<5%), it can cause serious aneurysm formations and/or occlusions in the entire vessels. When it involves the pulmonary arteries, it is one of the most important causes of morbidity and mortality. Hemoptysis is the main symptom.

Cardiac involvement is uncommon. Valvular lesions, myocarditis, pericarditis, coronary vasculitis, coronary and ventricular aneurysms, and intracardiac thrombus formation have been infrequently reported (6%), with a poor prognosis. Atherosclerosis is probably not increased in Behçet’s syndrome.

Central nervous system

Neurologic disease occurs in up to 10% of the patients. Most of the patients have parenchymal brain involvement (80%) affecting the brainstem. The prominent findings are pyramidal manifestations, followed by cerebellar and sensory symptoms and signs. Non-parenchymal disease (20%) is seen as intracranial hypertension due to dural sinus thrombosis manifested and presents by headaches and papilloedema. Parenchymal involvement has a more serious prognosis compared with non-parenchymal disease. Peripheral neuropathy is infrequent.

Other clinical features

According to one study, GI disease can occur in one-third of Japanese patients. It is less common, however, in Mediterranean countries. Mediastinal lymphadenopathy, pleural and pericardial effusions may be observed. Glomerulonephritis
is uncommon. Secondary amyloidosis is seen sporadically. Voiding dysfunction is reported, due to direct bladder involvement. Epididymitis is occasionally manifested.

**Diagnosis**

There are currently no laboratory tests available to make a diagnosis of Behçet’s syndrome. In 1990, the ISG published its diagnostic criteria based on data by a computer analysis of clinical features of 914 patients with Behçet’s syndrome and 308 diseased controls from seven countries around the world. These criteria had a sensitivity of 91% and specificity of 96%, with an improved discriminatory performance than the previous ones and have been validated in other patient populations. The recurrent oral ulceration is the mandatory finding, and two other findings must additionally be present from the repertoire of genital ulcerations, eye disease, skin lesions and a positive pathergy test, for diagnosis. Proper exclusions also should be performed.

**Differential diagnosis**

Herpes simplex virus infections, IBD, reactive arthritis, erythema multiforme, lichen planus, and autoimmune bullous disorders can be considered in the differential diagnosis. There are overlap syndromes of IBD, Crohn’s disease, and ulcerative colitis. Recurrent aphthous stomatitis, uveitis, erythema nodosum, and non-erosive arthropathy can accompany IBD. Recurrent aphthous stomatitis also is associated with IBD, but genital ulceration or scars are not features of these conditions. Pathergy test is usually negative in IBD.68

**Management**

Behçet’s syndrome runs a course with unpredictable exacerbation and remission periods, but the disease activity abates with time in many patients. The young and male patients have a more severe disease course and carry the risk for developing more severe complications compared with older and female patients. Ocular, vascular, and neurologic diseases cause the most serious morbidity. Although many patients with mild symptoms, especially older women, can be managed symptomatically, young and male patients with eye and vascular involvement should be treated more aggressively to prevent loss of vision and poor outcome. The treatment plan depends on the type and severity of symptoms, disease duration, and the age and sex of the patient. We first summarize the randomized, double-blind controlled studies and continue with a discussion of the European League against Rheumatism (EULAR) recommendations for the management of Behçet’s syndrome.

Colchicine is widely used for every lesion of Behçet’s syndrome, based on the findings of earlier open studies. In 1980, however, we showed for the first time that colchicine was useful only for erythema nodosum and arthralgia in males in a 6-month double-blind placebo-controlled study of 35 patients. As males have more severe disease than females, we conducted a 2-year placebo-controlled double-blind trial among a greater number of patients with active mucocutaneous lesions. When analyzed separately for each sex, colchicine 1 to 2 mg per day was effective only for genital ulcers, erythema nodosum, and arthritis among women, but only for arthritis among men. Side effects such as nausea, abdominal pain, and diarrhea were mild and did not differ from the placebo group. Our group studied azathioprine (AZA) 2.5 mg/kg per day among only male patients for eye and mucocutaneous lesions. This 2-year double-blind placebo-controlled study showed that AZA significantly decreased the attacks of hypopyon uveitis and the development of new eye disease among patients without eye involvement and preserved visual acuity. AZA was effective in controlling oral and genital ulcers and arthritis as well. Additionally, there was a tendency for preventing deep vein thrombosis. No serious side effects were observed attributable to AZA. It should be noted that AZA is usually underdosed in current clinical practice and for a beneficial response at least a regimen of 3 months is required. Additionally, an important observation is that early treatment with AZA also improves long-term prognosis of Behçet’s syndrome.73 It should also be kept in mind that combinations of AZA with interferon (IFN)-α should be avoided as they may cause severe leukopenia.

Thalidomide, both 100-mg and 300-mg daily doses against placebo, was studied for the oral and genital ulcers in a 24-week double-blind trial in male patients. Either dose of thalidomide was effective for significantly reducing the mean number of oral and genital ulcers and follicular lesions. An increase in erythema nodosum lesions in the thalidomide group was observed during the first 2 months compared with placebo, however. Also recurrences occurred when the drug was withdrawn. Well-known adverse effects are polynuropathy, teratogenesis, and sedation. In clinical practice, therefore, the use of thalidomide should be limited to patients with severe ulcers resistant to other treatments. It should be used for a short period of time and side effects should be closely monitored.

Cyclosporine-A, due to its rapid action, is usually the first-line agent in severe acute and sight-threatening eye involvement, especially with retinal vasculitis. It decreases the severity and frequency of ocular attacks, and improves visual acuity. It also has a beneficial effect on mucocutaneous lesions. Although in the original study, the dose of cyclosporin-A was 10 mg/kg per day, in current clinical practice the dose used is 5 to 3 mg/kg due to side effects such as hypertension, renal impairment, and neurotoxicity. Close monitoring is required even at low doses. Relapses can be observed after cessation of the drug. Cyclosporin-A and
AZA combinations usually are used in patients with resistant eye disease.

The only controlled trial of a nonsteroidal anti-inflammatory drug showed that azapropazone 300 mg three times a day for acute arthritis was not beneficial compared with placebo.66

Although corticosteroids are widely used for Behçet’s syndrome, the only placebo-controlled study with methylprednisolone acetate (40 mg intramuscularly, every 3 weeks) was conducted for genital ulcers.77 Men and women were analyzed separately. The trial showed that depot corticosteroids were useful only for erythema nodosum lesions among women but not in men, whereas there was no effect on genital ulcers, oral ulcerations, folliculitis, or arthritis.

Data on biologic agents come mainly from open studies with promising results in patients who are resistant to conventional treatments. IFN-α-2a, subcutaneously, 6 MU three times daily, decreased the mucocutaneous lesions in a placebo-controlled study but, unfortunately, no detail was given.78 In open studies IFN-α (3-6 MU/d) achieved a partial or complete response in most patients with severe posterior uveitis. Main drawbacks are high price and frequent side effects such as arthralgia, injection site reactions, fever, leukopenia, alopecia, and depression. These side effects are dose-dependent and require dose adjustment. Long-lasting remissions in patients with severe ocular disease have been reported after cessation of the drug.79,80 There is also accumulating evidence with tumor necrosis factor (TNF)-α blockers for other manifestations of Behçet’s syndrome such as severe uveitis, GI, neurologic, and vascular diseases that are resistant to conventional therapies. Infliximab 5 mg/kg was recommended as an add-on immunosuppressive therapy for patients who are intolerant or refractory to traditional immunosuppressives in a recent position paper.81 In the only placebo-controlled, double-blind study with a TNF-α blocker conducted by our group, etanercept was useful for most mucocutaneous lesions of Behçet’s syndrome, although it did not interestingly affect the pathergy and monosodium urate tests when used at 25 mg twice a week for a period of 4 weeks among only men.12 The main concerns with TNF-α blockers are high cost and the side effects such as an increased risk for bacterial infections and tuberculosis where Behçet’s syndrome is endemic.

Negative results with transfer factor82 and acyclovir83 but positive effects with dapsone for mucocutaneous lesions84 were reported in controlled trials with a limited number of patients and short durations.

EULAR has published recommendations for the therapy of Behçet’s syndrome. These recommendations for the uveitis, oro-genital ulcers, and arthritis are mainly evidence-based, whereas recommendations for other organs such as vascular, neurologic, and GI diseases are based largely on expert opinions and uncontrolled evidence from open trials and observational studies.85,86

We usually prefer cyclophosphamide (1000 mg, monthly intravenous boluses) with steroids (1000 mg intravenous boluses, three times every other day, followed by oral administration of 1 mg/kg) for pulmonary arterial disease, which has a high mortality rate if not treated.82 Surgical correction of pulmonary arterial aneurysms should not be attempted in this population, however, because of high surgical mortality.

It is noted that patients with peripheral arterial aneurysms should be treated with immunosuppressive agents similar to pulmonary artery aneurysms to prevent recurrence, before any surgical intervention.

As pulmonary embolism is rare and there is a risk for rupture of pulmonary artery aneurysm(s) that are frequently associated with the thrombophlebitis, we do not give anticoagulants, but prefer to use AZA and low-dose corticosteroids to suppress inflammation.

Local treatment for oral and genital ulcers is sufficient. An open study with a small number of patients suggested that oral lactobacilli-containing lozenges might be helpful for oral ulcers.87 Low-dose natural human IFN-α lozenges, however, did not have a beneficial effect for oral ulceration of Behçet’s syndrome in a formally conducted study.88 Variable results with other topical agents such as sucrafate, cyclosporin-A, and pimecrolimus cream have been summarized in more detail.89-91

Although we have made more progress during the recent decades for controlling the eye, mucosa-skin, and joint disease, more formal controlled studies are urgently needed for the vascular, neurologic, and GI involvement associated with Behçet’s syndrome.

The mean annual total cost per Behçet patient was US$ 3226 ± 3488 (SD); this was US$ 1180 ± 1053 for mucocutaneous-joint involvement, whereas for the neurologic disease it was much higher (US$ 5005 ± 2707).92

References


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