Treatment Options in Behcet's Disease

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Abstract: Behçet's disease (BD) is a chronic, relapsing, systemic vasculitis of unknown etiology with the clinical features of mucocutaneous lesions, ocular, vascular, articular, gastrointestinal, urogenital, pulmonary, and neurologic involvement. Mucocutaneous lesions figure prominently in the presentation and diagnosis, and may be considered the hallmarks of BD. Therefore, their recognition may permit earlier diagnosis and treatment. Although, the treatment has become much more effective in recent years, BD is still associated with severe morbidity and considerable mortality. The main aim of the treatment should be the prevention of irreversible organ damage. Therefore, close monitoring, early and appropriate treatment is mandatory to reduce morbidity and mortality. Traditional and current treatments with topical, paraocular and systemic corticosteroids, colchicine, dapsone, cyclosporine, azathioprine, methotrexate, cyclophosphamide and chlorambucil are summarized and recent insights into the pharmacology and effects of thalidomide, tacrolimus (FK-506), interferon-α, anti-TNF-α blocking monoclonal autoantibody (infliximab) and soluble TNF receptor (etanercept) are reviewed. We reviewed the current state of knowledge regarding the therapeutic approaches for BD and designed a stepwise, symptom-based, algorithmic approach, mainly based on controlled studies and our clinical experience in this field to provide a rational framework for selecting the appropriate therapy along the various treatment choices. Key clinical investigations with the status of ongoing clinical trials aimed at addressing the drug's efficacy, surgical care, and studies that have raised the possibility of new therapeutic uses are also presented. The challenges posed by the drug's teratogenicity and adverse effects are also considered, if present.

Keywords: Behçet's disease, diagnosis, treatment.

DEFINITION

Behçet's disease was first defined by Hulusi Behçet, a Turkish Professor of Dermatology, in 1937 as a triad of recurrent aphthous stomatitis, genital aphthae and relapsing uveitis [1]. During the ensuing 65 years multiple systemic associations of the disease including articular, vascular, gastrointestinal, cardiopulmonary and neurologic involvement have become increasingly apparent [2-14]. Although the etiology and pathogenesis is not clearly defined, genetic predisposition, infections and immunological dysfunctions have been implicated [5].

CLINICAL FEATURES

Mucocutaneous Lesions

Mucocutaneous features are the most common presenting symptoms of the disease; eye, vascular, pulmonary, gastrointestinal and neurological involvements are the most serious.

Oral Aphthae

Oral aphthae is localized, painful, and shallow, round to oval ulcers often covered by a gray fibromembranous slough and surrounded by an erythematous halo. They are seen as minor or major ulcerations, sometimes with herpetiform distribution at any site in the oral cavity. International study group criteria do not permit diagnosis in the absence of oral aphthae, and oral aphthae was seen in all patients with Behçet's disease. The vast majority of mild cases presents with recurrent aphthous ulcerations of the oral mucosa which are usually the earliest and universal sign of the disease that are indistinguishable from common aphthae—canker sores in appearance and localization and has a yellowish necrotic base. This is frequently the first symptom and can precede the other manifestations of the syndrome by many years. Minor aphthous ulcers (<10 mm in diameter) are the most common type; major or herpetiform ulcers are less frequent. Smokers often experience a relapse of oral ulcers after quitting and nicotine replacement patches have been suggested to be useful in Behcet' s disease [2, 4, 15, 16].

Genital Aphthae

In previous reports the prevalence of genital aphthae was found to be between 60 and 90%. Genital lesions were most commonly seen on the scrotum of male patients and on the vulva of female patients and tended to be larger and deeper in the female patients, sometimes even leading to perforations. The ulcers usually heal in 2–4 weeks; large ulcers frequently leave a scar whereas small ulcers and those on the minor labia heal without leaving a scar [2, 4, 15, 17].

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Erythema Nodosum-Like Lesions

Erythema nodosum-like lesions are tender erythematous nodular lesions that appear more commonly on the anterior aspects of the lower extremities and slowly resolve within a few weeks without scar formation. Erythema nodosum-like lesions generally resolve in pigmented ethnic groups with residual pigmentation, but recurrence is common. These lesions may also occur at other sites, including the buttocks, upper extremities, and less commonly on the face and neck [2, 4]. A great variety of histopathological changes can be seen in typical, well-developed erythema nodosum in patients with Behçet's disease. The histopathology of erythema nodosum lesions are mostly consistent with nodular panniculitis with vasculitis and neutrophilic infiltration is very common [18]. In previous reports the prevalence of erythema nodosum was reported as 15–78% and most authors reported a higher frequency of erythema nodosum in females [2, 15, 18, 19].

Papulopustular Lesions

Papulopustular lesions are situated mainly on the lower limbs and they are seen in as many as 34–70% of Behçet's patients. In the literature, some of the papulopustular lesions of Behçet's disease resembling the pustular lesions of acne vulgaris are called acneiform lesion of Behçet's disease. The pathogenesis of pustular lesions of Behçet's disease is different from those of acne vulgaris. The first one is a vasculitis while the second is a sebaceous gland disorder under hormonal factors. The pustular lesions of Behçet's disease are located more often on the lower part of the body, while the pustules of acne vulgaris are seen more frequently on the upper part of the body. Some authors have advised histologic confirmation that the papulopustular lesions are indeed vessel-based and neutrophilic. Most authors believe that those kind of vessel-based changes may only be secondary to inflammation and they are not considered as vasculitis. Some authors showed that there is a significantly higher frequency of papulopustular eruptions in males compared with females [2, 4, 12, 15].

Superficial Thrombophlebitis

Superficial thrombophlebitis is represented as palpable, painful subcutaneous nodules or string-like hardenings with reddening of the overlying skin especially on the lower extremities. In several studies thrombophlebitis was found to be present in 2.2–20% of Behçet patients. The higher prevalence of thrombophlebitis in males is confirmed in previous reports [2, 4, 15].

Pathergy Test

One clinically unique feature of the disease is hyper-reactivity of the skin to any intracutaneous injection or needle prick, which is known as pathergy. It is characterized by the formation of a sterile pustule or small papule 24–48 hours after an intradermal needle prick [2, 4]. At 24–48 hours, the puncture site becomes inflamed and the test is considered positive if there is an indurated erythematous small papule or pustule formation of more than 2 mm in diameter, which usually resolves within 3 or 4 days [21]. There are controversies about the histopathology of the pathergy reactions. Some authors found mixed infiltration, while others reported neutrophilic infiltration with leukocytoclastic vasculitis [12]. Mostly authors believe that there is no leukocytoclastic vasculitis in pathergy reactions [20, 21]. It was found high-pathergy positivity in the Mediterranean and Far Eastern countries (40–98%) [2, 4, 15, 18]. However test positivity is uncommon in individuals living in Western World, which reduces its diagnostic value in these countries [22]. The patergy test is more strongly positive in male patients [12, 23, 24]. Pathergy test was usually found during active phase in Behcet's patients with positive reaction [25]. However, the presence of a positive pathergy reaction is not associated with an increased risk for specific mucocutaneous or systemic manifestations of the disease, and does not predict a more severe disease course [24, 26]. Oral pathergy test was described by some authors like skin pathergy test [27, 28].

Other Skin Lesions

Other skin lesions, such as extragenital skin ulcers in the axillary and interdigital areas, Sweet's syndrome, pyoderma gangrenosum, leucocytoclastic vasculitis, palpable purpura, hemorrhagic bullae, fruncles, abscesses, erythema multiforme-like lesions, perniolike lesions, polyarteritis-like cutaneous lesions, true arterial lesions, subungual infarctions, are less common [14, 15]. Extragenital ulcers occur in about 3% of patients. They are common in children with Behcet's disease and these recurrent ulcers usually heal with mild scarring [15, 29]. Skin biopsies of extra-genital ulcerations showed vasculitis [29].

Systemic Manifestations

Ocular Involvement

Ocular involvement manifesting itself notably in the form of recurrent anterior and posterior uveitis and retinal vasculitis was noted in 29-80% of Behcet's

patients reported in the literature [2, 4]. The prevalence of ocular involvement was higher in male patients than in females [2]. Although the eye is the most commonly involved internal organ in Behçet's disease and is usually present from the outset, it typically occurs within 2 to 4 years of disease onset in a vast majority of clinical cases [30]. Ocular disease may be the initial manifestation of the disease in approximately one-fifth of cases. It occurs more commonly and severely among Japanese and Turkish patients [14, 30, 31]. Anterior uveitis with severe inflammation (hypopyon) observed in only a small group of patients with eye involvement indicates a bad outcome and is generally associated with severe retinal vasculitis. Isolated anterior uveitis is rare and also conjunctivitis is infrequent. Posterior uveitis with involvement of the retina can be severe, causing retinal exudates, haemorrhages, venous thrombosis, papilloedema and macular degeneration. Recurrent attacks of eye involvement result in structural changes, such as retinal scars and synechiae. These events eventually lead to loss of vision if left untreated [30, 31].

Musculoskeletal System Involvement

Articular involvement was reported to be present in approximately 30–70% of Behçet patients. It is mostly affecting the knees, ankles, wrists and elbows [2, 4]. Hulusi Behcet himself described joint involvement in 1938, a year after the original description. Joint disease is observed in around 50% of patients in the form of arthritis or arthralgia. It is usually mono- or oligarticular but can be symmetrical. Joint disease resolves in a few weeks and it seldom results in deformity and radiological erosions. Chronic arthritis and osteonecrosis are seen occasionally. Back pain is quite rare and controlled studies have not shown an increased sacroiliac joint involvement. Myositis can be seen in local or generalized forms [31].

Vascular Involvement

Deep venous thrombosis, arterial occlusions, and arterial aneurysms are found in 7–33% of Behçet patients according to the large series. Venous thrombosis affected the mainly lower limbs. Upper extremities, superior and inferior vena cava followed by dural sinus, jugular, renal, brachiocephalic and hepatic veins were less commonly involved. Arterial lesions were less frequently observed in Behçet patients, including occlusion of iliac and popliteal arteries and aneurysm of femoral, popliteal, iliac, pulmonary and carotid arteries. The prevalence of vascular involvement was found higher in male patients than

females [2, 4]. Pulmonary arterial aneurysms have a high mortality rate, especially with an aneurysm diameter of >3 cm. The main symptom is haemoptysis and these patients usually have associated thrombophlebitis and deep venous thrombosis [14].

Central Nervous System Involvement

Neuro-Behçet's disease occurs in 3.2–17% of Behçet patients. Neurologic involvement presents with central motor paresis, brain stem and cerebellar symptoms. Most patients have parenchymal brain involvement, which mainly affects the brainstem, manifested by the pyramidal, followed by cerebellar and sensory symptoms and signs, sphincter disturbances and behavioural changes. Neuro-Behçet's symptomes include headache, nausea, vomiting and/or ocular disturbances. Peripheral neuropathy, which is seen frequently in other vasculitides, is very uncommon. A high protein or cell count in cerebrospinal fluid examination implies a grave prognosis. Some patients develop psychiatric problems. Most common neurologic symptom among patients with Behçet's disease is headache. With descending frequency, headache, weakness, and alteration of consciousness and behavior were present in Behçet patients. The prevalence of neurologic involvement was times higher in males than females [2, 4, 14].

Gastrointestinal System Involvement

Gastrointestinal system involvement in Behçet's disease affects all areas from the esophagus to the anus. Most authors believe that the gastrointestinal system manifestations of Behçet's disease should be confined to aphthae, which can occur throughout the gastrointestinal system tract. The frequency of gastrointestinal system involvement varies considerably in different studies and also between different countries. In Japan and Korea the prevalence of gastrointestinal system involvement is higher (15–45%), whereas in Turkey and Israel the prevalence is much lower (0–5%). Some patients with inflammatory bowel disease have been included in series of patients with Behçet's disease. Gastrointestinal system ulcers were most commonly found in the esophagus, terminal ileum, colon and rectum, and no significant difference was noted in the frequency of gastrointestinal system involvement between the two sexes [2, 4]. The symptoms include anorexia, vomiting, dyspepsia, diarrhoea and abdominal pain. The ileocaecal ulcers have a distinct tendency to perforate. Intestinal ulcers in Behçet's disease are usually multiple and tend to perforate easily, which may lead to an emergency

operation. Hepatic problems are not common in Behcet' s disease unless an associated Budd–Chiari syndrome is present [14, 32].

Pulmonary Involvement

Pulmonary involvement occurs in 0.7–7% of Behçet patients. The various manifestations of vasculitis in the thorax include thrombosis in the superior vena cava, or mediastinal vein, aortic or pulmonary arterial aneurysm, pulmonary infarct, hemorrage, pleural effusion, focal or diffuse pulmonary fibrosis. Generally authors believe that vasovasorum vasculitis of pulmonary vessels is the pulmonary involvement of this disease as opposed to pulmonary parenchymal involvement, which can be a significant cause of death. It was noted a higher frequency of pulmonary involvement in males compared with females [2, 4].

Cardiac Involvement

Cardiac involvement is uncommon. However, sporadic cases have been reported with valvular lesions, myocarditis, endomyocardial fibrosis, pericarditis, intracardiac thrombosis, coronary vasculitis and ventricular aneurysms. Available data currently show that atherosclerosis is probably not increased in Behcet's disease, unlike rheumatoid arthritis and systemic lupus erythematosus [14, 32, 33].

Other Clinical Features

Other systemic features that may develop during the course of Behcet's disease with variable incidence are audio-vestibular, thoracic, renal and genitourinary [2, 4, 14, 30]. Unlike many other systemic vasculitides, glomerulonephritis is uncommon [14]. Amyloidosis of the AA type is seen sporadically [4]. Voiding dysfunction due to direct bladder involvement has been reported [34]. Epididymitis is seen in approximately 5% of the patients [35].

Relevant Investigations

Laboratory Studies

Although there is no specific laboratory profile to diagnose Behcet's disease, the key is to obtain maximal history and review of systems with detailed physical examination. A moderate anaemia of chronic disease, a slightly raised neutrophils and/or platelet count is found in around 15% of patients. The erythrocyte sedimentation rate and C-reactive protein are usually moderately elevated but do not correlate well with disease activity. Serum immunoglobulins, especially IgA and IgD, are sometimes elevated with the presence of circulating immune complexes; complement levels might also be high. Autoantibodies such as rheumatoid factor, antinuclear antibody, anticardiolipin and antineutrophilic antibodies are absent. Disease activity may be assessed by elevated status of neopterin, anti-streptolysin-O, α1-antitrypsin and α2-macroglobulin, all of which are the active components of phagocytic system of polymorphonuclear leukocytes. An elevation in the level of β2-microglobulin and myeloperoxidase, generated by activated neutrophils, have also been reported. Cryoglobulinemia, and eosinophilia may occur. HLA analysis should be performed for differential diagnosis in some cases. Abnormalities in the coagulation cascade such as increased levels of fibrinogen, plasminogen activator inhibitor-1 and circulating factor VIII have been described along with reduced fibrinolytic activity. Known thrombophilic factors such as factor V Leiden and prothrombin gene mutations and protein C and protein S deficiency also have been reported to coexist in Behçet's patients by us [36-38].

Skin Tests

Pathergy describes th inappropriately excessive subacute inflammatory reaction to non-specific injury. It is relatively specific for Behçet' s disease, although it can also be observed in Sweet syndrome, in a patients with chronic myeloid leukemia on treatment with interferon-α, erythema elevatum diutinum, pyoderma gangrenosum [2, 4].

In case of pyoderma gangrenosum on the other hand, there can be an increase in the size of the existing ulcer after trauma, which is more suggestive of Koebner phenomenon, rather than pathergy reaction [39].

The monosodium urate test has been found to be more sensitive than the formal pathergy test in the demonstration of abnormal inflammation in Behçet' s disease. The usual response to an intradermal injection of 2.5 mg of urate crystals is an erythematous reaction, maximal at 24 hours and mostly resolved at 48 hours. In Behçet's disease, the erythematous response is exaggerted, with a greater degree of inflammation present at 24 hours and/or persistance at 48 hours. This test has been reported as having a sensitivity of %61 and a sepsificity of %100 for the diagnosis of Behçet' s disease. The greater sensitivity of the urate crystal test suggests it has clear potential as an aid to the diagnosis of Behçet's disease, although a positive test may be difficult to demonstrate in patients on anti-inflammatory drugs [40].

Ocular Measures

A complete ophthalmic examination was performed by ophthalmologists with an interest in Behçet's disease. To evaluate ocular involvement, slit-lamp examinations and confirmation tests of retinal vasculitis were performed, such as angiography and scanning techniques [2, 4]. Ocular hemodynamic changes in patients with Behcet's disease can be evaluated by color doppler imaging, which demonstrates reductions in the blood flow values of the orbital arteries as a result of occlusive vasculitis. Ultrasonography may be helpful to assess the degree of vitritis. Optical coherence tomography may be useful in detecting and monitoring anatomically the foveal thickness in Behcet's disease patients with cystoid macular edema [30].

Radiologic Imaging and the other Tests

Although conventional chest radiography is commonly used for the initial assessment and may show mediastinal widening with vascular prominence in affected patients, especially in long-standing complete Behcet's disease patients, computed tomography is suggested to demonstrate the entire spectrum of thoracic manifestations of Behcet's disease, including abnormalities of the pulmonary artery vessel lumen and wall, perivascular tissues, mediastinal lymphadenopathy, lung parenchyma, pleura, and mediastinal structures. High-resolution computed tomography is sensitive in the demonstration of pulmonary changes in patients with Behcet's disease. End-expiratory high-resolution computed tomography examination is very useful and necessary to show the presence of air trapping, thus the presence of small airway disease, even if the patient is asymptomatic or has normal pulmonary function tests. Perfusion sintigraphy of the affected patients may reveal pulmonary perfusion defects. If indicated, magnetic resonance imaging is reportedly the most sensitive neuroradiologic approach to detect the focal lesions related to neuro-Behcet's disease and is superior to computed tomography in demonstrating vasculitic pattern of the disease. Double-contrast barium X-ray or endoscopy can detect gastrointestinal ulcers [41]. Long-latency reflexes is a useful technique to demonstrate subclinical neural involvement in patients with Behçet's disease [42]. In audio-vestibular evaluation, pure-tone audiograms may demonstrate subclinic or clinic sensorineural hearing loss in the low and high frequencies, specifically in older and complete Behcet's disease patients with longer disease duration [43, 44]. Bone mineral density in Behcet's disease might be slightly lower than in healthy subjects [45].

Relevant Differentials

In the absence of a universally accepted diagnostic test, the diagnosis of Behçet's disease remains purely clinical. In 1990, the International Study Group for Behçet's disease proposed new diagnostic criteria based on the analysis of 914 patients from several countries. For patients to be classified as having Behçet's disease, the patients must have recurrent oral ulcers plus at least two of the other criteria including ocular involvement, genital ulcers, skin lesions (erythema nodosum-like lesions and papulopustular eruptions) or the pathergy test in the absence of an alternative clinical diagnosis. It is important to note that a patient who fails to meet the criteria fully may still have Behçet's disease [46].

It usually is not difficult to recognize the fulfilling most of the diagnostic criteria of Behçet's disease, but the so-called incomplete forms sometimes cause problems. Therefore, other causes of oculomuco-cutaneous syndromes should carefully be excluded including autoimmune bullous skin diseases, erythema multiforme major, Reiter syndrome, seronegative arthropathies, sarcoidosis, Sweet syndrome, cicatricial pemphigoid, celiac disease, and pemphigus vulgaris. Similarly, herpes simplex virus infection, lichen planus, syphilis, systemic lupus erythematosus, ulcerative colitis, and mixed connective tissue diseases may also cause oral, cutaneous, and ocular lesions. Hughes-Stovin syndrome should also be differentiated and this syndrome consists of deep venous thrombosis often involving the caval vein accompanied by single or multiple pulmonary arterial aneurysms. Plausible alternative diagnoses such as seronegative arthropathies, rheumatoid arthritis, psoriatic arthritis, acute febrile neutrophilic dermatosis, familial Mediterranean fever, hyper IgD syndrome or periodic fever, pyoderma gangrenosum, multiple sclerosis, pulmonary embolism, and any cause of hemoptysis should be excluded. Oral ulcers alone should be differentiated from recurrent aphtous stomatitis, erythema multiforme, toxic epidermal necrolysis, syphilis, tuberculosis orificialis, inflammatory bowel diseases and erosive lichen planus. Genital ulcerations should be differentiated from venereal diseases such as chancroid, syphilis, scabies, and herpes simplex virus infection. Similarly, recurrent orogenital ulcera-tions are also seen in hypereosinophilic syndrome, myelodysplastic syndrome, Monchausen syndrome (pseudo-Behçet's syndrome), pemphigus vulgaris, tuberculosis cutis and acquired immunedeficiency syndrome. Anterior uveitis and iridocyclitis in Behçet's

disease should be differentiated from idiopathic uveitis, ankylosing spondylitis, Reiter syndrome, acquired secondary syphilis, primary intraocular lymphoma, lyme disease, Chron disease, herpes zoster ophthalmicus, Fuch heterochromic cyclitis, toxoplasmosis, toxocariasis, tuberculosis, tubulointerstitial nephritis, Kawasaki disease, sarcoidosis and inflammatory bowel diseases such as ulcerative colitis, Crohn disease, and Whipple disease, should also be excluded [2, 4, 14, 30].

TREATMENT

Treatment of the various symptoms of Behçet's disease remains controversial because of the heterogenity of the condition, lack of reliable laboratory markers of disease activity, and paucity of controlled clinical trials and unstandardized outcome measures for this disease.

Evidence Based Approach

Although the number of controlled trials has increased within the last decade, the treatment of Behçet' s disease remains empirical and cosiderable differences exist even among the experts in approaches to treatment. In this section, clinical studies were selected if they were randomized controlled trials, single- or double-blind, or interventions with pharmacological therapy compared to placebo or some other pharmacological agents.

Colchicine

Colchicine is an anti-inflammatory plant alkaloid and inhibits neutrophil chemotaxis by inhibiting the microtubule function. Colchicine has been used for the treatment of Behçet' s disease since 1975 [47]. Although colchicine is used widely for every lesion of Behçet's syndrome, it has been demonstrated that it is useful only for erythema nodosum and arthralgia. In a more recent, 2-year placebo- controlled, trial in a greater number of patients, colchicine 1.0–2.0 mg/day was beneficial only for genital ulcers, erythema nodosum and arthritis in women, and only for arthritis in men [48, 49]. The first double-blind study of colchicine, which involved 35 patients, was published in 1980. At 6 months only patients with erythema nodosum– like lesions and arthralgias benefitted from colchicines [48]. Another randomized double-masked trial with cyclosporine A versus colchicine in Behçet's patients showed that colchicine was less effective than cyclosporine A in improving the clinical manifestations of the disease [50]. In a study comparing the long-term effect of cyclophosphamide or colchicine on eye

involvement, no differences between treatment groups were observed [51]. The combination of cyclosporine A and colchicine in uveitis also was examined. The combination was effective at 6 months, but after 1 year recurrent uveitis attacks were observed [52]. In another recent trial the effect of colchicine on the extraocular manifestations was investigated in a 2-year double-blind study of colchicine versus placebo in 60 men and 56 women. Colchicine was superior to placebo among women only; perhaps this was related to the women's less severe disease [53]. It has effectively been used in placebo-controlled study for the treatment of active mucocutaneous and joint manifestations of Behçet' s disease without ocular or major organ involvement, because it is well tolerated at a dosage of 1.0–2.0 mg/day with the least risk and side effects, especially among women [2]. Although colchicine may be used in anterior uveitis at a dosage of 1 mg/day, its efficacy for severe posterior ocular disease is questionable [53]. Indeed, it should not be used alone for posterior uveitis or retinal vasculitis because there is no positive finding by randomized trial showing the efficacy of colchicine in such cases. To the contrary, it has been found to be inferior to cyclosporine A in a doublemasked open trial by Masuda *et al.* [50]. However, colchicine may be used in combination with cyclosporine A. In general, dapsone and colchicine are used for mild to moderate mucocutaneous Behçet's disease, whereas cyclosporine A and other immunosuppressives can be reserved for Behçet's patients with severe systemic or ocular disease. Simple measures such as rest, analgesics, and nonsteroidal anti-inflammatory drugs with or without colchicine (0.5–1.5 mg/day) are effective for most cases of Behçet's patients arthritis in both sexes. In resistant cases, benzathine penicilline, low-dose corticosteroid and azathopurine may be used.

Colchicine is widely used in Japan and is very effective. We believe that the low frequency of ocular and neurologic involvement in our patients may be result of the beneficial effect of the colchicine therapy we initiated at the time of diagnosis, early in the course of the disease at population. The variable responses observed may reflect the different populations studied [2, 4].

Azathioprine

Azathioprine is a mercaptopurine derivate and inhibits purine ring synthesis. Azathioprine 2.5 mg/kg/day decreased hypopyon uveitis attacks and the development of new eye disease in patients without eye involvement, and preserved visual acuity in a 2-year, controlled trial [54]. Azathioprine was also

beneficial for oral and genital ulcers, for arthritis and possibly for preventing deep vein thrombosis [55]. However, azathioprine is usually underdosed and for a beneficial response at least 3 months is required. Early treatment with azathioprine also improves the long-term prognosis [56].

The first well-controlled trial of azathioprine in Behçet's patients, published in 1990, was a 2-year randomized, placebo-controlled, double-blind study of 75 men. One group included 25 patients (12 receiving azathioprine and 13 placebo); the second group included 48 patients (25 receiving azathioprine and 23 placebo). Orogenital ulcers and arthritis improved with azathioprine. Additionally, eye inflammation was controlled with azathioprine, and unilateral eye disease was prevented from becoming bilateral. The concomitant corticosteroids dosage was tapered successfully with azathioprine. Re-evaluation of these patients, who had been enrolled an average of 8 years, confirmed the effectiveness of azathioprine and showed that early treatment favorably affected the long-term prognosis of Behçet' s disease. However, the beneficial effect of azathioprine did not extend to those patients who had longstanding eye disease (2 years or more) when they first started using azathioprine [54]. Azathioprine (orally, 2.5 mg/kg/day or 50–150 mg/day, once daily or in divided doses), alone or in combination with other immunosuppressives, reduces the incidence, frequency, and severity of ocular disease, and has a favorable effect on arthritis and orogenital ulcerations when compared with placebo in a large randomized, placebo-controlled trial. Indeed, early treatment with azathioprine is effective in controlling the attacks of posterior ocular inflammation and vasculitis, improving the long-term visual prognosis of the disease with prevention of new eye disease [54, 56].

Azathioprine– corticosteroid combination therapy has also been shown to be effective in pulmonary arterial aneurysms with demonstrated clinical and radiological regression. It was shown that 2 pulmonary artery aneurysms, 1 carotid artery aneurysm, and 1 superior vena cava syndrome developed in placebo groups, while the azathioprine groups did not show any large vascular involvement. Thus, azathioprine may be beneficial when arteries and veins are involved. Azathioprine monotherapy, however, is rarely indicated for mucocutaneous disease, although it does not affect papulopustular lesions [55].

The patients should be followed for gastrointestinal disturbances and be monitored by a complete blood count every month and liver function test every 3 months for bone marrow suppression and hepatotoxicity, respectively. Combinations of azathioprine and interferon-α cause severe leucopenia and should be avoided [30].

Although methods of treatment have improved, prevention is still an issue. The question arises whether prophylactic immunosuppressive therapy should be given to young men with recent disease onset; long-term prospective studies are needed to provide the answer. A comparative study of ocular disease included 29 patients who were randomly enrolled to receive azathopurine and 115 patients who were treated with pulse cyclophosphamide. Azathipurine was more effective in treating uveitis, but retinal vasculitis improved more with cyclophosphamide [57]. Thus, azathioprine alone or in combination with other immunosuppressive drugs provides substantial symptomatic relief and may prevent some major complications. The researchers suggested that azathioprine could be useful as a steroid sparing drug.

Cyclosporine

Cyclosporine-A is a calcineurin inhibitor and naturally occurring product of fungi with more specific effect on the immune system than corticosteroid and cytotoxic drugs. The primary effect of cyclosporine-A is the inhibition of T lymphocyte activation and recruitment, which is safer than cytotoxic agents because it does not induce permanent immunosuppression [30]. As a rather quick-acting agent, cyclosporine-A is usually the treatment of choice for sightthreatening and progressive uveitis, especially with retinal vasculitis. In a controlled study, cyclosporine-A 10 mg/kg reduced the frequency and severity of ocular attacks, improved visual acuity and also decreased the mucocutaneous lesions [50].

As a randomized and blinded study, 218 patients with Behçet's disease were enrolled, and the duration of treatment ranged from 8 days (local therapy) to 3 years. Cyclosporine-A was compared with conventional therapy (corticosteroids and chlorambucil) in 2 studies. Other studies compared cyclosporine-A with colchicine, cyclophosphamide and Orabase [58-61]. Improvement in the cyclosporine-A treated group, particularly in eye inflammation, was shown in 4 studies. In one study, orogenital ulcers and arthritis improved more with conventional therapy than with cyclosporine-A [58]. A blinded trial of cyclosporine-A versus monthly bolus cyclophosphamide in active, potentially reversible, eye disease showed that visual acuity improved

significantly in the cyclosporine-A group during the initial 6 months. However, after 2 years (after 6 months the trial was unmasked) the beneficial effect was not sustained [61]. In a randomized trial with topical cyclosporine-A and Orabase (as placebo), there were no differences in oral ulcer outcome between these 2 groups [60]. In a recent trial, the combination of cyclosporine-A with colchicine was effective in reducing the number of uveitis attacks at the end of 6 months, but at 12 months several patients had increased frequency of uveitis attacks [52]. Many randomized, controlled, and masked trials compared cyclosporine-A with conventional therapy (corticosteroid and chlorambucil) and colchicine. The duration of treatment was between 3 months and 3 years. The results demonstrated that cyclosporine-A, alone (5–10 mg/kg/day) or in combination with corticosteroids, is an effective treatment of almost every manifestation of Behçet's disease, particularly in ocular inflammation, decreasing the frequency and severity of exacerbations with improved visual acuity. It was also found to be more effective than monthly bolus cyclophosphamide in the initial phase of the disease. Although about half of the patients with mucocutaneous disease improved from cyclosporine-A therapy, orogenital lesions and arthritis improved more with conventional therapy than with cyclosporine-A in one study [52, 58-61].

As a result, cyclosporine-A, at an initial dosage of 5 mg/kg/day, is the most rapidly acting drug for acute uveitis. Cyclosporine-A is frequently combined with azathioprine in resistant cases. The combination of cyclosporine-A with azathipurine gives a significantly better outcome in ocular inflammation than monotherapy. However, most patients develop a disease flare after drug discontinuation. Relapses can occur after its cessation. It is now used at 5 mg/kg or at lower doses due to side effects, and even at these doses close monitoring is required for hypertension, nephrotoxicity and neurotoxicity. The long-term use of cyclosporine-A is limited by the development of neurological side effects, hirsutism, gingival hyper-plasia, gastrointestinal disturbances, breast tender-ness, hyperglycemia, hepatotoxicity, and hypertension (25%). In addition, cyclosporine-A -related nephroto-xicity, which occurs in about 75% of cases, is a very serious complication and should never be underestimated. Therefore, the maintenance of its blood level is held between 50 and 150 ng/ml and monitoring should involve blood pressure, complete blood count, and liver and renal function tests every 6 weeks [30].

Thalidomide

Thalidomide, a cyclic derivate of glutamic acid, was manufactured in the early 1950s. It was withdrawn from the world marketplace for 4 decades because its devastating congenital birth defects were recognized. However, a new chapter has begun with its approval by the Food and Drug Administration. Indeed, thalidomide has recently been attracting interest as a potential therapeutic option in Behçet' s disease with its reported immunomodulatory, anti-inflammatory, and anti-angiogenic properties. It reduces phagocytosis by neutrophils, inhibits neutrophil migration into the site of inflammation, and down-regulates the production and activity of proinflammatory cytokine TNF-α across a broad range of cell types by accelerating the degradation of its messenger RNA. Moreover, it is also a potent co-stimulator of human T lymphocytes, which is more pronounced in CD_8 than in CD_4 lymphocytes. Based on these findings, the plausible mechanism of action and its clinical usefulness in Behçet's disease are by reducing TNF-α production or by promoting T cell responses without inhibiting normal immunity [62-69].

Thalidomide 100 mg daily was effective for reducing the number of oral and genital ulcers and papulopustular lesions in a 24-week study. Recurrence is usual when the drug is withdrawn [62]. Low dosage of thalidomide (50 mg/day) has been found to be effective in the majority of Behçet's patients with papulopustular eruption and orogenital ulcers [68]. Likewise, it is found to be useful in neuro-Behçet's disease, pyoderma gangrenosum, recurrent and perforating intestinal ulcers, and colitis. The usual oral dosage of the drug is between 100 and 300 mg/ day orally for 1 to 6 months [62-71]. A cross-over randomized trial compared thalidomide with placebo, each given for 2 months in 73 patients. Oral ulcers improved with 100 mg of thalidomide daily but flared after the cessation of therapy. Treatment with thalidomide (studied in 96 men for 6 months in a double-masked trial) showed that 100 mg daily was equally effective to 300 mg daily and was superior to placebo in controlling the mucocutaneous lesions. However, lesions promptly recurred with discon-tinuation of therapy, and activation of erythema nodosum also was observed [62]. An analysis of the efficacy of thalidomide on the ocular manifestations of these patients showed that those allocated to placebo had more frequent and severe attacks of uveitis than those treated with thalidomide [72]. In pediatric cases, a complete remission was obtained in an infant with

Behçet's disease, allowing the immunosuppressives to be gradually withdrawn [74]. The drug was maintained for 1 year with no recurrence of the disease. Adverse effect was not observed. Similarly, thalidomide was found to be effective in doses between 1 mg/kg/week and 1 mg/kg/day with a complete remission of oral ulcers in patients with Behçet's disease who were unresponsive to other immunosuppressive drugs [75].

Side effects such as polyneuropathy, teratogenesis and sedation limit its use to patients with treatment-resistant severe ulcers for short periods and with close monitoring. Although genital ulceration was markedly improved both in frequency and severity, prednisolone or colchicine may be added to achieve adequate control in some cases. However, thalidomide is not recommended as a first-line therapy for self-limiting mucocutaneous symptoms, especially in female patients. Thalidomide is restricted to men or to women who have undergone hysterectomy or bilateral tubal ligation. Drug side effects and symptom recurrence soon after the discontinuation of treatment limit its use. Moreover, its effects on the eye and joint are not clear. Furthermore, a consideration of thalidomide therapy demands a careful weighing of both benefits and risks because teratogenic and neuropathic side effects continue to be of grave concern. Sedation, exacerbation of erythema nodosum, somnolence, dizziness, constipation, headache, nausea, weight gain, edema, rashes, dry mouth, and papulovesicular transient eruptions may occur. Taking thalidomide at bedtime, in turn, can minimize somnolence, dizziness, and morning hangovers [30, 76, 77].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Azapropazone

The efficacy of the nonsteroidal anti-inflammatory drug, azapropazone, 300 mg t.i.d., was no different for acute arthritis than for placebo in a controlled study. This randomized, double-blind, placebo-controlled study was conducted in which 28 patients with active arthritis of up to 10 days' duration were treated with azapropazone. Twenty-nine patients received placebo, and both groups were treated for 3 weeks. At the end of the observational period, there were no differences between the 2 groups. Azapropazone provided only analgesia during the first week of its use. The results of this trial confirmed previous experience suggesting that NSAIDs are of little benefit in the arthritis of Behçet's disease [78]. No other controlled trials with non-steroidal anti-inflammatory drugs have been done in Behçet's disease. In an open trial, 5 patients with

Behçet's disease-associated arthritis were treated with oxaprozin, and improvement of arthritis and erythema nodosum was reported. In a second open trial, indomethacin was given to 15 patients with arthritis. Improvement was observed in 80% of those with articular manifestations, in 43% with oral aphthae, in 38% with genital ulcers, and in 88% with cutaneous lesions. However, the clinical evaluation of joint involvement was not described. These variable results probably reflect the different populations studied and the dosages of individual NSAIDs used [79-81].

Interferon

Because interferon has immunomodulatory properties, an increase in the activity of T lymphocytes and natural killer cells may be helpful in the elimination of foreign antigens. Viruses and bacteria have been proposed as etiologic agents in Behçet's disease. Interferons are natural defenses against viruses, bacteria, and tumors that act to enhance protein synthesis Therefore, interferon was given to patients with Behçet's disease [30].

Interferon-α-2a, subcutaneously, 6 million IU three times a week, significantly decreased the duration and pain of oral ulcers and the frequency of genital ulcers and papulopustular eruptions compared with those observed in the pre-treatment period. Although its effect started rapidly, all symptoms recurred during the post-treatment follow-up. In uncontrolled studies, interferon is effective for both ocular and extraocular symptoms of Behçet's disease, and long-lasting remissions have been reported after stopping the drug. Its high cost and frequent side effects limit its widespread use [76, 77, 82].

Zouboulis and Orfanos showed in their large series that 95% of ocular Behçet's patients exhibited a partial or complete response to interferon-α. Interferon-α2a regimens were suggested to be more effective than interferon-α2b on ocular manifestations [81]. Alpsoy *et al* reported in their randomized masked trial that both severity and frequency of ocular attacks improved in about 83% of patients treated with interferon-α2a at a dosage of 6 million IU subcutaneously three times a week for 3 months, although the number of their patients was limited. It also reduced the pain and duration of oral ulcers compared with placebo [83]. Calguneri *et al* demonstrated that 96% of their Behçet's patients who were resistant to previous conventional treatments responded well to interferon-α treatment. The dosage was 5 million IU subcutaneously three

times a week, which was tapered to 3 million IU three times a week after 6–9 months. Overall, 76% of ocular Behçet's patients demonstrated a complete remission. In addition, remission was also obtained in 90% of cases with vascular disease, and 100% in both arthritis and neurological diseases, although flu-like symptoms were recorded in eight patients [84]. It reduces the frequency of arthritic attacks, genital ulcers, and papulopustular lesions and decreases the duration of oral ulcers with complete or partial responses in the majority of cases. Although the mean frequency and duration of erythema nodosum-like lesions and thrombophlebitis were also decreased, the differences were not significant. A recent study by Kotter *et al* have shown that interferon-α2a is beneficial for the extraocular manifestations of the disease, such as genital ulcerations, arthritis, and skin lesions, although only 36% of oral ulcers has responded [85]. Similarly, interferon-α produced remission in neurological and vascular Behçet's patients with no recurrence or major toxicity during the long-term follow-up [84, 86]. In a multicenter study of 28 patients, all patients with uveitis, mucocutaneous lesions, arthritis, and gastrointestinal vasculitis improved. In a randomized double-blind trial, topical interferon α–2c hydrogel was not beneficial for the oral ulcers of Behçet's disease [87]. In studies of interferon to date, recurrence of symptoms on cessation of treatment is observed. Side effects are frequent, e.g. flu-like symptoms, fever, arthralgia, injection-site reactions, leucopoenia, alopecia and depression. There is no standard dose for interferon-α. Once such a dose is agreed on, properly controlled studies can be designed. Until then the efficacy of interferon -α in Behçet's disease is unknown.

Anti-TNF Agents

Tumour necrosis factor (TNF)-blocking agents such as infliximab, etanercept and adalimumab have been reported to have had some success in more than 300 patients with various lesions, e.g. eye, mucocutaneous, gastrointestinal and neurological disease, and even pulmonary artery aneurysms. In these reports, the most commonly used anti-TNF agent has been infliximab. The recommendations in a recent position paper include it as an add-on immunosuppressive therapy for selected patients with Behçet's disease, who are refractory or intolerant to traditional immunosuppressives. A single infusion of infliximab (5 mg/kg) can be used as a first agent for sight-threatening uveitis. The initial response is fast, e.g. within 24 hours, but relapses can necessitate continuous treatment. In the

only placebo-controlled study of any anti-TNF agent in Behçet's disease, etanercept significantly decreased the mean numbers of oral ulcers, nodular and papulopustular lesions [88-91].

Clinical use of infliximab in ocular Behçet's disease was first described in 2001 [88], and recent randomized and controlled trials are encouraging. Infliximab is a human-murine chimeric anti-TNF IgG1 monoclonal antibody [90]. It binds to human TNF-α and neutralizes its activity. Indeed, cytokines derived from T helper type-1 lymphocytes, including TNF, have been demonstrated to participate during the course of Behçet's disease In addition, increased numbers of monocytes and T lymphocytes that overproduce TNF have also been shown in patients with active Behçet's disease. Moreover, TNF receptors in the peripheral blood as well as TNF concentrations in the circulation have been found to be increased in active Behçet's patients [30]. Recent studies on infliximab have shown rapid and effective suppression of almost all manifestations of both systemic and ocular Behçet's disease, at least in the short term. In non-ocular cases, infliximab may be an effective and novel therapy for orogenital ulcerations, erythema nodosum, arthritis, gastrointestinal disease, cervical esophageal perforation, and recalcitrant cerebral vasculitis in neuro-Behçet's disease with an immediate and dramatic resolutions of both organ-specific and systemic symptoms [90]. Robertson and Hickling treated a Behçet's patient with orogenital ulceration unresponsive to known treatment modalities. Infusions of 5 mg/kg infliximab at 0, 2, and 6 weeks resulted in being free from ulcerations [92].

Etanercept is a dimeric fusion protein of the p75 kD TNF-α receptor and Fc portion of human IgG1. It is produced by recombinant DNA technology, has a good tolerability, and is administered by subcutaneous injection [93]. Etarnercept has been found to be effective on mucocutaneous manifestations of Behçet's disease in a randomized, double-blind, placebo-controlled study. The numbers of oral ulcers, nodular and papulopustular skin lesions, as well as episodes of arthritis have been found to be decreased. The probability of being free from oral ulcers and nodular lesions was also demonstrated to be higher in etanercept group, though it did not affect the pathergy reaction [89]. However, another study has indicated that no response is observed on orogenital ulcerations and erythema nodosum lesions in patients with Behçet's disease, which responded to infliximab afterward [94, 95]. High cost and side effects, such as

an increased risk of tuberculosis and other infections, are still concerns with anti-TNF agents.

Corticosteroids

Corticosteroids produce a broad and non-selective suppression of the immune system and act by the inhibition of cyclo-oxygenase and lipo-oxygenase pathways. By inhibition of phospholipase A2, corticosteroids reduce arachidonic acid formation, and, therefore, prostaglandins, leukotriens, and thromboxane. In addition, it decreases lymphocyte migration and chemotaxis, circulating monocytes, macrophage activity, as well as the levels of complement and interleukins [30].

Corticosteroids are the most widely used drugs for the management of Behçet's disease, although controlled studies are lacking. In a recent, controlled study we tested the efficacy of depot corticosteroids, 40 mg methylprednisolone acetate against placebo in patients with skin-mucosal disease. In this trial, depot corticosteroids were useful for controlling erythema nodosum lesions in female, but not male, patients [96].

A palliative effect and even shortening of the duration of oral aphthae and genital ulcers have been seen with topical application of corticosteroids. The preferable types are the high-potency class I and class II corticosteroids in a gel base. For more severe ulcers, intralesional administration of triamcinolone acetonide may be helpful. Creams containing corticosteroids with antibiotics can be applied to genital ulcers. Systemic administration of corticosteroids is indicated for severe mucocutaneous disease [15]. In one study, the combination of corticosteroids and azathioprine had a beneficial and rapid action on orogenital ulcerations, arthritis, and vasculitis [97]. In monoarthritis with a large effusion, intra-articular injection or systemic administration of corticosteroids may be beneficial [98]. The use of corticosteroids in neuro-Behçet's disease is warranted when vasculitis is suspected. Pulse methylprednisolone also is beneficial in patients with increased intracranial pressure [99-101]. Corticosteroids in combination with immunosuppressive drugs is indicated in severe cases of Behçet's disease [102]. Complete resolution of hemoptysis and radiologic signs of pulmonary artery aneurysms were observed after treatment with corticosteroids. A persisting remission was noted after 10 months [103]. In mild uveitis, administration of corticosteroids eye drops controls the inflammation. However, in severe uveitis and in retinal vasculitis, high dose systemic corticosteroids in combination with immunosuppressive drugs is indicated. The efficacy of corticosteroids monotherapy in Behçet's disease uveitis was disappointing. However, corticosteroids mono-therapy is used in cases in which immunosuppressive drugs are contraindicated, such as in pregnancy. In severe exacerbations of the disease, high-dose corticosteroids combined with cyclophosphamide may be required [30, 102].

Dapsone

Dapsone was beneficial for mucocutaneous lesions in Behçet's disease. Dapsone is an anti-infective drug with anti-inflammatory properties, modifying neutrophil chemotaxis with antioxidant properties. A 12-month, double-blind, placebo-controlled, cross-over clinical trial has demonstrated that oral dapsone at a dosage of 100 mg/day is associated with a significant improvement in orogenital ulcers and cutaneous manifestations in Behçet's disease [104]. Dapsone was given to 30 patients in an open trial, particularly for severe skin lesions, and improvement improvement was reported [105]. However, another brief report showed that dapsone did not modify the disease course in most patients [106]. Although dapsone may be given for persistent mucocutaneous manifestations, it is rarely administered for the treatment of Behçet's disease.

Other Drugs

In controlled studies, transfer factor, aciclovir and daclizumab were not effective in Behçet's disease [107-109]. However, these trials were done with a limited number of patients and were of short duration [110-148].

Therapy of Types /Condition

Mucocutaneous Lesions

In mild forms of the mucocutaneous disease, initial treatment consist of mild diet, and avoidance of hard, spicy or salty nutrients and chemicals. Topical treatment of oral ulcers includes caustic solutions (silver nitrat %1-2, tinctura myrrhae %5-10 w/v, hydrogen peroxides %0.5, methyl violet %0.5) 1-2x/day, topical antiseptic and anti-inflammatory drugs (amlexanox %5 in oral paste, rebamipine, hexetidine %1, chlorhexidine %1-2 mouth-wash solutions, benzydamine, camomile extracts, tetracycline mouth-wash) and also glycerine solution 250 mg/5 ml glycerine for 2 min, 4-6x/day, topical corticosteroids (triamcinolon mucosal ointment, dexamethasone mucosal paste, betamethasone pastilles) 4x/day or

during the night or intrafocal infiltrations with triamcinolone suspension 0.1-0.5 mL per lesion, topical anaesthetics (lidocaine %2-5, mepivacaine %1.5, tetracaine %0.5-1 gels or mucosal ointments) 2-3/day, topical sucralfate (suspension, 1gr/5mL) 4x/day, 3 months durations as mouthwash, topical aminosalicylic acid (%5 cream) 3x/day [15-149, 150]. In daily practice, the contents of a tetracycline capsule (250 mg) can be dissolved in 5 ml of water, holding in the mouth for about 2 minutes (four times a day). Behcet disease patients with insufficient oral intake caused by pain can be treated with topical lidocaine (2–5%) applications before meals and oral anti-inflammatory rinses containing chlorhexidine gluconate (1–2%) [152].

In topical treatment of genital ulcers and cutaneous lesions, corticosteroid and antiseptic creams can be applied for a short period of time like 7 days. Painful genital ulcers can be managed by topical anaesthetic in cream [15]. Topical sucralfate reduces the healing duration and pain of genital ulcers like oral ulcers. Sucralfate has been used in the treatment of orogenital ulcerations [151]. For severe ulcers, intralesional corticosteroid (triamcinolone acetonide) may be helpful. Corticosteroid injections like triamcinolone 0.1-0.5 mL/lesions can be focally applied in recalcitran ulcerations [15]. Bacanli *et al*. studied the efficacy of topically applied granulocyte colony-stimulating factor in the treatment of oral and genital ulcers. It decreased the healing time and pain of both ulcers in 6 of 7 patients compared with the pretreatment period. The effectiveness of the treatment, however, did not continue during the posttreatment period [32]. In a randomized, controlled, crossover double-blind trial, zinc sulfate treatment decreased the mucocutaneous manifestations index after the first month of therapy. After shifting to placebo treatment, the clinical index started to increase but remained significantly lower than levels before therapy [32].

In severe forms of the mucocutaneous type of th disease, additional systemic treatment is required. The following drugs have proven beneficial: Corticosteroids (prednisolone, initial dose 30-60 mg/day p.o. for at least 4 weeks) can be administered as monotherapy or in combination with colchicine [15] (1-2 mg/day p.o.), dapsone (100-150 mg/day p.o.) [104], interferon-α (3-12 million IU/3xweek s.c.) [30] or azathioprine [54] (initial dose 100 mg/day p.o.). Nonsteroidal anti-inflammatory drugs, like indomethacin [80] (100 mg/day p.o. over 3 months) can be effective on the mucocutaneous lesions. Pentoxifylline (300 mg 1-3x/day p.o.) and oxypentifylline (400 mg 3x/day p.o.)

treatment for 1 month induced a remission of oral ulcers. Pentoxifylline decreases superoxide production by neutrophils [136]. High dosage of oral or pulse intravenous steroids may be indicated for large and refractory mouth ulcers larger than 10 mm or when the oropharynx is compromised. Severe mucocutaneous disease and arthritis may be treated with systemic corticosteroids in combination with azathioprine [54, 55].

Colchicine (0.5-2 mg/day p.o.) can be used as a second-line alternative treatment. A recent randomized double-blind and placebo controlled study has shown that colchicine reduces the occurence of genital ulcers and erythema nodosum among women. Colchicine inhibits the enhanced chemotactic activity of neuto-phils. Colchicine seldom eliminates oral ulcerations completely, but may reduce to an acceptable level the frequency and severity of oral ulcer [48].

There is little evidence that antibacterials or antivirals are useful in the therapy of mucocutaneous lesions.There is some evidence that adjunctive penicilline treatment may enhance the clinical response to colchicine therapy for both oral and genital ulcers [129]. It has been proposed, although not proven, taht an etiologic relationship exists between streptococcal infection and Behcet' s disease. In an uncontrolled study, benzathine penicillin improved the clinical manifestations of disease. Patients with mucocu-taneous lesions had complete recovery in 5 to 20 days. In an retrospective study, benzathine penicilline had a beneficial effect on oral and genital ulcers. However no meaningful effects effects were seen on other lesions. A prospective randomized study compared the efficacy of colchicine with colchicine and benzathine penicillin over 24 months. The number of arthralgia episodes was significantly reduced in the combination group and episode-free period was significantly prolonged with combination therapy. And they reported the effectiveness of benzathine penicilline and colchicine on the mucocutaneous manifestations, benefits not achieved with colchicine monotherapy [129, 130]. The result of an open study with minocycline treatment for 3 months were reported and it was observed that oro-genital ulcers, erythema nodosum and papulopustular eruptions improved at a rate of %10 to 100 [131]. We already reported that erythromycin treatment appears to be an effective treatment option in erythema nodosum-like lesions in Behcet's disease. The hypothetical antiinflammatory effects of erythromycin, besides its antibiotic properties, explain such a clinical improvement [133].

Dapsone (100-150 mg/day p.o.) also inhibits the enhanced chemotactic activity of neutrophils and can be used as an alternative drugs to colchicine. Quick relapses have been found after discontinuation of dapsone treatment. Intermittant ascorbic acid treatment (vitamin C; 500mg/day) is advisable to prevent increased methaemoglobin serum levels. Its use is often complicated by haemolytic anemia, even in patients with normal glucose-6-phosphate-dehyro-genase activity [105, 106].

Interferon-α has beee-n successfully used in the treatment of Behcet' s disease. Its immunomodulatory effect, ability to augment the decreased activity of the patient's natural killer cells, capacity to intibit neovascular proliferation, and antiviral activity have been suggested to explain its action in Behçet' s disease. It was shown to markedly inhibit IL-8 synthesis and secretion form endothelial cells. Interferon-α-2a treatment at dose of 6 million IU/3 x week s.c. for 3 months, is an effective alternative treatment, particularly for management of mucocutaneous lesions [82-85].

Azathiopurine (2.5 mg/kg body weight/day p.o.) has been found to be an effective choice in oral and genital ulcers in a randomized, double-blind and placebo controlled study [54].

Cyclosporin A (3 mg/kg/day p.o.) is capable of markedly ameliorating mucocutaneous lesions. But, it should be reserved for the most severe patients because of its significant long-term adverse effects [30].

Methotrexat (7.5-20 mg/1x weekly p.o. over 1 month) is able to induce an improvement of a severe mucocutaneous involvement [122].

Thalidomide (100-300 mg/day orally., optimal dose 100 mg/day in the evening for 8 weeks) has been approved for the treatment of male and sterilised or post-menapausal women with Behcet' s disease. Thalidomide was shown to selectively inhibit TNF-α synthesis by monocytes [30]. In a randomized, double-blind placebo controlled study with 63 Behcet's patients, a remission of oral and genital ulcers, as well as papulopustular eruptions was detected in %24 of the patients over 2 months. During the 6-months treatment, %30 of the patients with Behçet' s disease remained free of mucocutaneous lesions. Discontinuation of the treatment results in oral and genital ulcers recurrences; therefore a maintenance treatment with 50 mg/day to 50 mg twice a week is recommended. Thalidomide is often highly effective at reducing the frequency and severity of mucocutaneous disease resistant to colchicine. However, its widespread use is clearly limited teratogenic and neuropathic complications. The risk of developing irreversible peripheral neuropathy is thought to increase in a dose-dependant fashion, and so thalidomide should be recommended at the lowest dose possible to control symptoms, e.g. 50 mg daily or 100 mg 3 times a week. Since thalidomide can be sedating, it is best taken at night [62-66].

Recent studies of anti-TNF agents such as infliximab (i.v. 0, 2, 4, 8. months), and etanercept (s.c. twice a week) have shown favorable results [88, 89, 94, 95].

Lactobacilli, which have antiinflammatory activity, may be useful in some diseases, particularly in inflammatory bowel disease. In a study aimed at evaluating the efficacy of lactobacilli lozenges in the management of oral ulcers of Behcet's disease, a significant decrease in the mean number of ulcers was found following treatment, especially among women [157].

Ocular lesions

Since ocular inflammation in Behçet' s disease is associated with significant morbidity, management should be in close collaboration with an experienced medical opthalmologist. Short-lived attacks of anterior uveitis can be managed with topical corticosteroids, either by eye drops or *via* orbital floor injections. Topical mydriatic agents are also given for attacks of anterior uveitis. Nonsteroidal anti-inflammatory drugs, such as topical indomethacin, diclofenac, and flurbiprofen, may prove useful as potentiators of corticosteroid activity, which allows corticosteroid dosage to be reduced and when the use of corticosteroids is contraindicated [30, 36, 37].

Prolonged episodes, or if posterior uveitis is present, should be treated with systemic corticosteroids, often using doses up to 1 mg/kg of prednisolone daily. Although oral corticosteroids alone has a palliative effects on ocular attacks, it doesn' t improve the visual prognosis and can even lead to secondary cataracts and retinal vein thrombosis. Steroid sparing agents are generally instituted early in the course of significant ocular inflammation and may have to be used in combination to gain control of ocular disease [36, 37]. Azathiopurine, 2-2.5 mg/kg/day, is effective at inducing remission and preventing disease

and preventing disease progression, and is now generally thought of as the first-line of management in ocular Behçet' s disease [36]. Cytotoxic agents such as azathiopurine, chlorambucil, and cyclophosphamide help prevent ocular attacks in approximately %50-70 of Behçet' s patients. In a single study, the rate of complete and partial remissions was %50 with corticosteroids, %66 with colchine, and %71 with azathiopurine. In an uncontrolled study, colchicine was beneficial for ocular inflammation [37]. We believe that the low frequency of ocular involvement in our patients may be result of the beneficial effect of the colchicine therapy we initiated at the time of diagnosis, early in the course of the disease [2, 4]. Azathiopurine and chlorambucil have also been reported to improve the long-term visual prognosis [57-113].

Cyclosporine A, 2.5-5 mg/kg/day, is also safe and effective for treating ocular manifestations but should be avoided if neurological manifestations of Behçet's disease are present. Because cyclosporine may cause worsening of neurological symptoms. Mycophenolat mofetil has shown promise as an effective drug for managing uveitis refractory to treatment with azathiopurine and/or cyclosporin, usually at a dose of 1 gr in ocular involvement. Tacrolimus, at a dose of 100-200 µg/kg/day, has similar efficacy to cyclosporin A in the treatment of refractory ocular Behçet' s disease [30].

Several groups have reported success in the treatment of Behçet's disease with TNF-α blockade, including infliximab and etanercept. The effect of TNF-α blockade reported in patients with Behçet's disease was striking. Infliximab was effective for treating relapsing panuveitis. Most lesions refractory to conventional treatments entered remission within a few weeks of TNF-α blockade. After termination of anti-TNF therapy, however, they recurred within several months in most cases. Adverse effects of anti-TNF agents in Behçet's disease were not negligible. These include serious infection, including tuberculosis, autoantibody production, and other respiratory, gastrointestinal, and dermatological symptoms. Nonetheless, anti-TNF agents are promising in those with symptoms refractory to conventional treatments [30, 88, 89, 94, 95].

Study of interferon-α for Behçet' s disease have shown encouraging results. In one study, %95 of ocular Behçet's patients had a response to therapy with interferon-α. Interferon-α2a is most effective for ocular symptomes, in one study, it resulted in complete remission of ocular symptomes in %67 of the patients within four months. In uncontrolled studies, interferons are effective for ocular symptoms of Behçet' s disease, and long-lasting remissions have been reported after stopping the drug. Its high cost and frequent side effects limit its widespread use. Side effects are also frequent, e.g. flu-like symptoms, fever, arthralgia, injection- site reactions, leucopoenia, alopecia and depression [30, 83-85].

Intravenous infusions of immuneglobulins, plasmapheresis, and granulocytapheresis have also been tried in small numbers of patients, but the data are quite limited [148]. In an open prospective study, the efficacy of selective granulocytopheresis in patients with refractory uveoretinitis of Behcet's disease was assessed. Fourteen patients were treated, each received one session/week over 5 consecutive weeks. Nine patients improved but the condition of five patients did not change. It seemed that patients who had had Behcet's disease for a long time were better responders [148].

Arthritis

Nonsteroidal antiinflammatory drugs and colchicine are effective for most cases of arthritis in Behçet' s patients. Sulfasalazine can also be used, but other types of standart disease modifying anti-rheumatic drugs (DMARDS) or methotrexate are rarely used [93]. Low-dose corticosteroids and azathiopurine are used in patients whose arthritis is resistant to treatment with nonsteroidal antiinlammatory drugs, colchicine or sulfasalazine. Interferon-α is also highly effective [83-85]. Fatigue and fibromyalgia-like symptoms are frequently reported in Behçet's disease and generally respond to conventional fibromyalgia regimes, e.g. daily selective serotonin reuptake inhibitors along with low dose nocturnal amitiriptyline (25-50 mg nightly) [36]. Benzathine penicillin had also a beneficial effects on arthritis [129]. Arthrocentesis and intra-articular steroid injections may also be effective for severe monoarthritis [30].

Entero-Behçet' s Disease

The treatments used for inflammatory bowel disease including sulfasalazine and corticosteroids are also useful for the gastrointestinal lesions of Behçet' s disease. The dose of corticosteroids depends on the severity of lesions. Bowel rest is obligatory in patients with an acute abdomen and bleeding. Surgery is considered for patients with bowel perforation and persistan bleeding. Invazive surgical procedures often result in excessive infiltration of inflammatory cells into

the treated tissues, with subsequent anastomotic leakage. To prevent this complication, indetermine doses of corticosteroids are given to the patients for several days after surgery. Even if the operation is successful, repeated operation because of recurrence is required in about half of the patients. There was a suggestion that azathiopurine use was helpful. The rate of reoperation can be lowered by using azathopurine in patients with entero-Behçet' s disease. Intra-arterial steroid injections into the mesenteric arteries were found to be effective in severe entero-Behçet' s disease unresponsive to conventional treatments [30, 93].

Neuro-Behçet's Disease

Central nervous system lesions constitute one of the most-serious symptoms. Central nervous system lesions are usually treated with high-dose corticosteroids. High doses of corticosteroids are administered during the acute phase of neurologic involvement, with subsequent tapering of the dose. Pulsed corticosteroid therapy is an alternative. Corticosteroids can be supplemented with cytotoxic agents such as cyclophosphamide, chlorambucil, and methotrexate [93]. Methotraxate which inhibits folic acid metabolism and then decreases synthesis of nucleic acids [30]. It was applied to patients with progressive neuro-Behçet's Disease (progressive dementia or psychosis) by low-dose weekly administration (7.5–12.5 mg/week) for 12 months. Low-dose weekly methotrexate therapy may be a choice for treating steroid refractory neuro-Behçet's disease [126]. Aseptik acute meningitis or meningoencephalitis in the early phase of the disease responds well to treatment with corticosteroids. In contrast, chronic progressive central nervous system disease is resistant to all the currently available therapies [93]. In one study, %20 of patients with chronic neurologic involvement died within seven years [101].

Angio-Behçet' s Disease

The correct management of thrombosis in patients with Behçet's disease is still unknown. Arteritis is treated with combination of corticosteroids and cytotoxic agents. Anticoagulants and antiplatelet agents are used for deep venous thrombosis, together with short-term administration of intermediate doses of corticocteroids. Anticoagulation initially with heparin and then warfarin, is recommended, although thrombotic episodes may recur or progress despite anticoagulation. No controlled studies had been done comparing the anticoagulant or immunosupressive

agents, intensity or duration of therapy required for vascular complications. The decision when to withdraw anticogulation needs to be based on the individual clinical situtation. Anticoagulant drugs should be given carefully in patients with pulmonary vessel disease because of the risk of potentially fatal hemoptysis. Half of patients die within three years after the onset of hemoptysis [36].

Surgical treatment may be considered for refractory large-vessel involvement. Isolated aneurysmal disease should be treated, where feasible, by surgical repair because of the high risk of rupture. However, as with all surgery in Behçet' s disease, control of inflammation prior to surgery is highly desirable to prevent postoperative complications. Immunosupressive treatment, in combination with corticosteroids, is indicated postoperatively to prevent relapse.

Behcet disease patients should carefully be scanned for possible multiple aneurysms in the pulmonary artery, abdominal aorta as well as in the iliac, femoral, and the popliteal arteries. In such cases, surgical treatment or stent-graft insertion should be performed, when feasible, for non-pulmonary arterial aneurysms because of a high risk of rupture. However, proper timing is essential and the possibility of an anastomotic aneurysm developing after surgery should be kept in mind. Similarly, invasive surgical procedures generally result in excessive infiltration of inflammatory cells into the treated areas with delayed wound healing at operative sites and subsequent anastomotic leakage despite any form of therapy. Most arterial complications of angio-Behçet' s disease present with a pseudo-aneurysm rupture or with impending rupture of primary abdominal aneurysms with critical limb ischemia, which may necessitate amputations [30-36]. Segmental stenosis of the inferior vena cava can be treated with percutaneous transluminal angioplasty [30]. An uncontrolled, open study reported the efficacy of cyclosporin in the treatment of the thrombophlebitis of Behçet's disease [76].

Cardiac Involvement

Anticoagulant or thrombolytic therapies including heparin, warfarin, streptokinase have been generally considered as the first choice of treatment of intracardiac thrombus of Behçet' s disease [38]. Our policy is to anticoagulate patients with thrombosis in the conventional manner with a short period of warfarin therapy (e.g. 3-6 months) while at the same time instituting immunosuppressive therapy including

corticosteroids, azathiopurine and cyclophosphamide [36-38]. Surgical treatment is reported to be unsuccessful in most of the patients. A single center has reported prothetic valve detachment or suture detachment requiring reoperation in 4 of 11 Behçet's patients after aortic valve surgery. These postoperative complications are probably related to the heightened inflammatory response of Behçet's patients to simple trauma, known as the pathergy reaction [33, 36, 37].

Renal Involvement

Current treatment options for renal Behçet's disease are not evidence based. Radiological renal vascular intervention combined with immunosuppressive drugs can be useful in selected cases. Peritoneal hemodialysis and even renal transplantation may be indicated if the patient develops end-stage renal failure [158, 159].

Therapy of types /condition and Floor Chart of 1 st 2nd 3rd line medicine Topical Treatments

Treatment	Dose	Used as first-line therapy	Used as alternative therapy
Triamcinolone acetonide ointment	3 times a day topically	Oral and genital ulcers	
Betamethasone ointment	3 times a day topically	Genital ulcers	
Betamethasone drops	1-2 drops 3 times daily topically	Anterior uveitis, retinal vasculitis	
Dexamethasone	1.0-1.5 mg injected below Tenon's capsule for an ocular attack	Retinal vasculitis	
Methyl prednisolone acetate	Anterior parabulbar sub-Tenon capsule injection 1 ml every 2-4 weeks	Anterior uveitis	
%0.5-1 tropicamide drops	1-2 drops once or twice daily topically	Anterior uveitis	
%0.5-1 cyclopentolate drops	2-3/ day topically	Anterior uveitis	
Prenisolone	5 mg in 20 ml water	Oral ulcers	
%5 Amlexanox paste	4/day topically	Oral ulcers	
Sucralfate suspension	4/day topically for 3 months	Oral and genital ulcers	
Triamcinolone acetonide 40 mg ampule	Intralesionally 5 mg/ml	Severe oral and genital ulcers	
Lidocaine %2-5	4/day topically as mouthwashes, before meals	Severe and multiple oral ulcers in Behçet's patients with insufficients oral intake by pain,	
Chlorhexidine gluconate rinses %1-2	Topically as mouthwashes	Oral ulcers	
Tetracycline	250 mg in 5 ml water solution, held in mouth for 2 min once a day		Oral ulcers
rhGM-CSF 300 µg ampule	Intralesionally injection in every 2 weeks		Large genital ulcers

Systemic Treatments

Treatment	Dose	Used as first-line therapy	Used as alternative therapy
Prednisolone	5-20 mg/day orally		Erythema nodosum, anterior uveitis, retinal vasculitis, arthritis
Prednisolone	20-100 mg/day orally	Gastrointestinal lesions, acute meningo-encephalitis, chronic progressive central nervous system lesions, arteritis	
Methylprednisolone	1000 mg/day for 3 days iv.	Acute meningo-encephalitis, chronic progressive central nervous system lesions, arteritis	Gastrointestinal lesions, venous thrombosis
Colchicine	0.5-1.5 mg/day orally	Oral and genital ulcers, pseudofolliculitis, erythema nodosum, anterior uveitis, retinal vasculitis	Arthritis

Thalidomide	100-300 mg/day orally		Oral and genital ulcers, pseudofolliculitis.
Dapsone	100 mg/day orally		Oral and genital ulcers, pseudofolliculitis, erythema nodosum
Pentoxifylline	300 mg/day orally		Oral and genital ulcers, pseudofolliculitis, erythema nodosum, leg ulcers
Levamisole	150 mg in 3 doses/day every 2 dayx1 week		Mucocutaneous lesions
Penicilline	1.2×10^6 U/3 week		Mucocutaneous lesions, arthritis
Azithromycin	500 mg 3 times a week for 4 weeks		Mucocutaneous lesions
Azathopurine	100 mg/day orally		Retinal vasculitis, arthritis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Chlorambucil	5 mg/day orally		Retinal vasculitis, acute meningo-encephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Cyclophosphamide	50-100 mg/day orally		Retinal vasculitis, acute meningo-encephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Cyclophosphamide	700-1000 mg/month iv		Retinal vasculitis, acute meningo-encephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Methotrexate	7.5-15 mg/week orally		Retinal vasculitis, arthritis, chronic progressive central nervous system lesions
Cyclosporine	5 mg/kg of body weight/ day orally	Retinal vasculitis	
Interferon-α	5 million U/day im or s.c.		Retinal vasculitis, arthritis, mucocutaneous lesions
Indomethacin	50-75 mg/day orally	Arthritis	
Sulfasalazine	1-3 gr/day orally	Gastrointestinal lesions	Arthritis
Warfarin	2-10 mg/day orally	Venous thrombosis	Arteritis
Heparin	5 000-20 000 U/day s.c.	Venous thrombosis	Arteritis
Aspirin	50-100 mg/day orally	Arteritis, venous thrombosis	Chronic progressive central nervous system lesions
Dipyridamole	300 mg/day orally	Arteritis, venous thrombosis	Chronic progressive central nervous system lesions
Surgery			Gastrointestinal lesions, arteritis, venous thrombosis
FK506 (Tacrolimus)	0.05-0.20 mg/kg/day orally in 2 divided doses		Severe posterior uveitis
Infliximab	3-10 mg/kg, 1-4 infusions within a 6 month period		Severe posterior uveitis
Combination therapies			
Corticosteroids + cyclophosphamide	Cyclophosphamide 750-1000 mg/month		Severe exacerbations, uveitis, central nervous system vasculitis, severe large vessel vasculitis

Cyclosporine A + azathiopurine + corticosteroids	Cyclosporine A 3-5 mg/kg/day, azathiopurine 2.5 mg/kg/day		Severe uveitis
Azathiopurine + colchicine	Azathiopurine 2.5 mg/kg/day, colchicine 1.5 mg/day		Uveitis
Penicilline + colchicine	Penicilline 1.2×10^6 U/3 week, colchicine 1.5 mg/day		Mucocutaneous lesions + arthritis

Manifestations	Treatments
Oral apthae	1st line: Topical triamcinolone acetonide, prednisolone, amlexonax, anti-inflammatory rinses, topical anaesthetics 2nd line: Topical sucralfate, aminosalicyclic acid, caustic solutions, oral tetracycline solutions, colchicine, levamisole, thalidomide, pulse methyl prednisolone, intralesional trimcinolone acetonide 3rd line: Cyclosporine, azathiopurine, methotrexate, chlorambucil, infliximab, etanercept, plasmapheresis-apheresis, zinc sulphate, penicilline, azithromycin, minocycline, dapsone, pentoxifylline, interferon-α
Genital ulcers	1st line: Topical triamcinolone acetonide, sucralfate, oral colchicine, azathiopurine, dapsone, prednisolone 2nd line: Levamisole, interferon-α, methotrexate, thalidomide, cyclosporine A
Papulopustular eruptions	1st line: Topical bethametasone, oral colchicine, azathiopurine, dapsone, prednisolone 2nd line: Levamisole, dapson, interferon-α, , thalidomide, azitromycin, pentoxifylline
Erythema nodosum	1st line: Oral colchicine, dapsone, prednisolone 2nd line: Indomethacin, Dapson, interferon-α, thalidomide, azithromycin, erythromycin
Articular involvement	1st line: Indomethacin, oxaprozin, analgesics and the other nonsteroid antiinflammatory drugs, sulphasalasine, azathiopurine, oral colchicine, prednisolone, intrarticular triamcinolone acetonide injections and arthrocentesis. 2nd line: Methotrexate, dapson, interferon-α, thalidomide, cyclosporin A, azathiopurine + cyclosporin A 3rd line: DMARDs, serotonin reuptake inhibitors, amitiriptyline
Central nervous system involvement	1st line: Oral corticosteroids + azathiopurine, pulse iv methyl prednisolone, oral prednisolone 2nd line: Oral or pulse iv cyclophosphamide, chlorambucil, methotrexate, azathiopurine
Cardiovascular disease, arteritis, and venous thrombosis	1st line: Oral or pulse iv cyclophosphamide, azathiopurine, pulse iv methyl prednisolone, oral prednisolone, aspirin, sc or iv heparin, oral or iv warfarin, i.v. streptokinase 2nd line: Dipyridamol, corticosteroid + cyclophosphamide. 3rd line: Surgery, percutaneous transluminal angioplasty, cyclosporine A
Thoracic involvement	1st line: Oral prednisolone + pulse iv cyclophosphamide 2nd line: Pulse iv corticosteroid + pulse iv cyclophosphamide 3rd line: Anti-TNF agents
Epididimoorchitis	1st line: Oral prednisolone, colchicine, nonsteroid antiinflammatory drugs 2nd line: Cyclosporine A
Uveitis	1st line: Topical corticosteroids eye-drops and ointments, mydriatics/cycloplegics, β-blockers, α_2-agonists, oral colchicine, oral prednisolone, cyclosporin A, azathiopurine, intravitreal and parabulbar sub-Tenon capsule injections. 2nd line: Pulse iv methyl prednisolone, oral methotrexate, carbonic anhydrase inhibitors, chlorambucil, topical NSAIDs 3rd line: Infliximab, etanercept, interferon-α, thalidomide, Tacrolimus, corticosteroids + cyclophosphamide, azathiopurine + colchicine, cortocisteroids + cyclophosphamide + azathiopurine, i.v. immunoglobulins, plasmapheresis, granulocytopheresis, mycophenolate mofetil.
Gastrointestinal involvement	1st line: Sulfasalazine, corticosteroids 2nd line: Cyclosporine A, azathiopurine, surgery 3rd line: İntraarterial corticosteroids injections
Renal involvement	1st line: Corticosteroids, azathiopurine, cyclophosphamide, cyclosporine 2nd line: Peritoneal hemodialysis, renal surgery and renal transplantation

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