Treatment of Behçet's Disease

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Behçet's disease is characterized with multifactorial etiopathogenesis and multiclinical pictures. The treatment of patients with Behçet's disease is based on the severity of illness, and the most appropriate management of Behçet's disease requires a multidisciplinary approach. Although various therapeutic modalities have been employed for Behçet's disease, treatment is far from satisfactory. Treatment of Behçet's disease includes local, systemic, or surgical therapies. Limited success has been found with colchicine, azathioprine, indomethacin, cyclophosphamide, chlorambucil, levamisole, transfer factor, fibrinolytic therapy, and systemic corticosteroid. New therapeutic approaches have been introduced for Behçet's disease using cyclosporine, thalidomide, interferon, acyclovir, high-dose corticosteroids or cyclophosphamide pulse therapy, and FK 506. We suggest that therapeutic agents should be selected after thorough evaluation of the immune state of each patient by using various tests and by determining any aggravating or provoking factors involved. In general, a combination-agent regimen is more effective than a single-agent regimen. Early diagnosis and proper treatment can inhibit or at least slow the progress of the disease remarkably.

Key Words: Behçet's disease, treatment

Behçet's disease is a chronic, systemic disease which manifests itself as recurrent, multiple lesions in many organs including the mucous membrane, eye, skin, joints, cardiovascular system, central nervous system, and gastrointestinal tract (Shimizu et al. 1979).

The pathogenesis of the disease is still unknown and the diagnosis of Behçet's disease is based on clinical grounds because there are no pathognomonic laboratory features.

Although multiple therapeutic modalities have been employed for Behçet's disease, treatment is far from satisfactory.

Treatment of Behçet's disease seems to be symptomatic and empirical. Most studies have been troubled by factors such as the variability in the natural course of the disease and the limitations in the number of cases for clinical investigation.

These factors have caused difficulties in evaluating therapeutic efficacy, thus resulting in poorly-controlled studies.

A postal survey of 17 management problems sent to 21 international experts who were aware of the variations of the disease led to considerable discrepancies in the responses (Yazici and Barnes, 1989).

Limited success has been found with colchicine, azathioprine, indomethacin, cyclophosphamide, chlorambucil, levamisole, transfer factor, fibrinolytic therapy, dapsone, and systemic corticosteroid (Wong et al. 1984; Arbesfeld and Kurban, 1988; O'Duffy, 1988; Yazici and Barnes, 1991).

In recent studies, new therapeutic approaches have been introduced for Behçet's disease using cyclosporine, thalidomide, interferon alfa, interferon gamma, acyclovir, high-dose corticosteroids or cy-
clophosphamide pulse therapy, and FK506 (Wechsler and Godeau, 1993).

This article is an overview of all kinds of therapeutic modalities including local and systemic agents which have been used for Behçet’s disease. Our therapeutic principles will also be introduced on the basis of our clinical experience in the treatment of about 4,700 Korean patients with Behçet’s disease.

Local therapy

Tetracycline. Although the mode of action is uncertain, tetracycline remains the drug of choice for aphthous stomatitis and oral ulcers of Behçet’s disease (Lehner, 1977). Tetracycline has antibacterial, antymyospasmal, antiviral, and antichemotactic effects. The patient should dissolve the contents of a 250 mg capsule in 5 ml of water or flavored syrup and hold the solution in the mouth for about 2 minutes before swallowing; this is repeated four times daily. Another report recommended that the contents of a 250 mg capsule should be dissolved in approximately three-quarters of a cup (180 CC) of water because a more-concentrated solution prepared from capsules may erode or stain the enamel of the teeth (Burgess et al. 1990). An alternative to tetracycline is cephalixin (250 mg dissolved in 30 ml water). Tetracycline syrup can also be used in combination with diphenhydramine hydrochloride, which provides a topical anesthetic effect (Balciunas et al. 1991).

Steroid. Topical corticosteroids are effective for oral or genital ulceration if they are applied during the prodromal stage of ulceration. The most widely used preparations for oral ulceration are triamcinolone cream 0.1% in Orabase, 2.5 mg tablets of hydrocortisone sodium succinate, or 0.1 mg tablets of betamethasone valerate (Lehner, 1977). The combination of antibiotic plus corticosteroid may be effective in reducing the severity of episodes of genital ulceration (Yazici and Barnes, 1991).

Dexamethasone elixir (0.5 mg/5 ml) is used as a rinse and then expectorated, or 0.5 mg tablets are allowed to dissolve slowly close to the oral ulcers twice daily. Beclomethasone dipropionate aerosol can be used four times daily (2 puffs/application or approximately 84 μg) for minor aphthous oral ulceration (Thompson et al. 1989). Patients with large major oral or genital ulcers may be treated by intralesional triamcinolone acetonide, 10 mg/cc into the base of the ulcer from the adjacent mucosa. When topical benzocaine 20% is applied first, this is not too painful. Such treatment is often effective for large ulcers (Conklin and Blasberg, 1991). Not all topical oral corticosteroids are safe; for example, betamethasone disodium phosphate in much smaller doses particularly seems prone to cause adrenal suppression (Lehner and Lyne, 1969).

Patients also should be monitored regularly for candidiasis and/or treated prophylactically with appropriate antifungal agents (Brown and Bottomley, 1990).

Uveitis and ocular inflammation may respond to treatment with topical mydriatics and corticosteroids (Lehner, 1977).

Other Drugs. Lidocaine gel(2%) may relieve the severe discomfort of oral ulcerations. Chlorhexidine used as a mouth wash may have palliative or even therapeutic effects (Addy et al. 1974). Benzoylamine rinse offers only very temporary anesthesia and can cause sensitization (Motley, 1988).

Carbenoxolone sodium mouth wash produces slight improvement only (Poswillo and Partridge, 1984). Silver nitrate sticks have been used for years, despite the discomfort of application. However, they seem to have little effect on the duration of the symptoms. It has been suggested that a 5% silver nitrate solution applied by a Q-tip may be better tolerated, but this has not been proven to be effective (Conklin and Blasberg, 1991).

Sucralfate suspension can be used for the treatment of oral ulcerations. It is believed to act primarily at the ulcer crater and to form a protective coat that shields the lesion (Rattan et al. 1994). Sucralfate suspension has a proven therapeutic value in the treatment of duodenal ulcer, reflex esophagitis and the prevention of stress induced gastrointestinal bleeding (Tryba and Mantey-Striers, 1987; Barker et al. 1991). Amlexanox (C16 H14 N2 O4) is a topical anti-inflammatory, antiallergic drug. Topically applied, 5% amlexanox was introduced as an effective drug in reducing aphthous ulcer’s erythema, pain, and lesional size (Greer et al. 1993).
Systemic therapy

Corticosteroids. Corticosteroids have long been the mainstay of treatment for all the various clinical manifestations of Behçet’s disease including mucocutaneous, ophthalmic, neurologic involvements, and progressive thrombophlebitis (O’Duffy and Goldstein, 1976; Wong et al. 1984).

We experienced that the administration of pulse corticosteroids can rapidly suppress symptoms and signs of meningoencephalitis, including pleocytosis, fever and headache, as well as other abnormal parenchymal neurologic signs in severely affected neuro-Behçet’s disease patients (Bang et al. 1996). Intrarticular steroids may be helpful for the treatment of localized active arthritis (Arvesfeld and Kurban, 1988).

Although they have a beneficial effect on acute manifestations, there is no definite evidence that they are effective in controlling progression of Behçet’s disease.

The disease may progress even while corticosteroids are being used, and corticosteroids seem to have little effect on chronic and late sequelae.

Therefore, systemic corticosteroids must be used cautiously in controlling variable clinical manifestations of Behçet’s disease, and the steroid side effects which can result from long-term use must be considered.

In some cases, it may be ideal to use low-dose systemic corticosteroids in combination with other immunosuppressive agents, especially for chronic recurrent manifestations (Diming and Perkins, 1975; Betti et al. 1976; Yazici and Barnes, 1991).

Chlorambucil. Mamo and Azzam reported in 1970 that chlorambucil was effective in treating uveitis in Behçet’s disease. In 1984, O’Duffy et al. also experienced the effectiveness of chlorambucil in the treatment of uveitis and meningoencephalitis of Behçet’s disease.

Chlorambucil is a bifunctional alkylating agent that is structurally related to nitrogen mustard. How it reduces inflammation in Behçet’s disease and other inflammatory diseases is unknown (O’Duffy et al. 1984).

The most worrisome immediate toxicity is bone marrow suppression (Rudd et al. 1975).

In high doses it tends to suppress all hematopoietic stem cell lines (Stukov, 1975). Furthermore, at the bone marrow suppression fails to improve spontaneously or may evolve into acute myelogenous leukemia (Cameron, 1977; Berk et al. 1981). Therefore, serious toxicity limits the use of this drug despite its proven therapeutic efficacy.

An initial daily dosage of chlorambucil is 0.1 mg/kg, and a maintenance dosage is 2 mg/day.

Azathioprine. Azathioprine at a dose of 2.5 mg/kg/day was shown to be superior to placebo in a 2-year double-blind study (Yazici et al. 1990).

It was demonstrated that azathioprine was effective in maintaining visual acuity and, perhaps more importantly, in preventing the development of new eye manifestations. This drug also has been shown to be effective in preventing the development of new aphthous ulcerations.

Serious toxicity, however, includes sterility, myelotoxicity, immunosuppression, opportunistic infection and liver disease (Steinberg et al. 1972).

Azathioprine exerts an anti-inflammatory effect by suppressing both cellular and humoral immune responses (Corley et al. 1966).

As with other immunosuppressives, azathioprine may be useful as a steroid-sparing agent.

Cyclophosphamide. The clinical spectrum of activity for cyclophosphamide is very broad and similar to that of nitrogen mustard.

Cyclophosphamide at a dose of 2- to- 3mg/kg/day was shown to be effective in patients with Behçet’s disease who were resistant to corticosteroids and had not responded to levamisole (Davatchi et al. 1984). Patients responded well, particularly in regard to articular, cutaneous, and genital manifestations, with minimal toxicity.

Pulse cyclophosphamide (1,000 mg) which was given intravenously once monthly was well tolerated and produced a significant improvement in patients with severe posterior uveitis, or neurologic involvement (Jorizzo and Rogers III, 1990; Davatchi, 1991).

Low dose pulse cyclophosphamide was also shown to be an effective method of treatment in ophthalmologic lesions of Behçet’s disease with extremely rare side effects. It was given as an intravenous bolus of cyclophosphamide at 500 mg/m² of body surface (Shahram et al. 1993).

Others have found cyclophosphamide most help-
ful in combination with prednisone for oral ulcers and visual disturbance (Buckley and Gillis, 1969). The clinical toxicity of cyclophosphamide differs from that of nitrogen mustard in that significant degrees of thrombocytopenia are much less common but are a more frequent occurrence of alopecia. Patients should be forewarned of this possible event, which is usually reversible even without interruption of therapy. As one of the side effects, the occurrence of sterile hemorrhagic cystitis must be considered.

For routine clinical use, ample fluid intake and frequent voiding are recommended. Administration of the drug should be interrupted at the first indication of dysuria or hematuria.

Colchicine. Colchicine exerts its therapeutic action by inhibiting polymeronuclear chemotaxis, which is thought to be overactive in Behçet's disease (Matsumura and Mizushima, 1975). Colchicine interferes with the function of the mitotic spindles and causes depolymerization and disappearance of the fibrillar microtubules in granulocytes and other motile cells. This action is apparently the basis for the beneficial effect of colchicine, namely, the inhibition of the migration of granulocytes into the inflamed area (Insel, 1991).

Conflicting reports regarding the efficacy of colchicine have been published. A dose of 1mg per day of oral colchicine, given for 2 months to 2 years, was useful in treating cutaneous and ocular manifestations (Miyachi et al. 1981). Another study showed 0.6mg twice daily for 5 weeks had a remarkable improvement of cutaneous, ocular and gastrointestinal manifestations (Raynor and Askari, 1980). A retrospective study of 157 patients with Behçet's disease receiving colchicine 0.5mg one-to-three times per day for more than 1 year showed that about 70% of patients were improved (Mizushima et al. 1977). But another double-blind controlled study reported no effect of colchicine on oral aphthous ulcer, genital lesion or eye lesion. However it was useful in controlling erythema nodosum and arthralgias (Aktulga et al. 1980). In a recent study of 32 patients with Behçet's disease who had a cutaneous manifestation, arthritis and uveitis, colchicine was effective in 66% of the patients (Kotter et al. 1996).

Nausea, vomiting, diarrhea, abdominal pain, oligospermia, amenorrhea or dysmenorrhea, general malaise and hair loss have been reported as side effects of colchicine. Hematologic side effects are rare consisting of granulocytopenia, agranulocytosis, thrombocytopenia and aplastic anemia (Malkinson, 1982).

FK506 (Tacrolimus). FK506 is a new immunosuppressive agent isolated from the fermentation broth of Streptomyces tsukubaensis (Kino et al. 1987). The agent has been shown to have immunosuppressive activities similar to those of cyclosporine. A long-term FK 506 therapy in Behçet's disease was effective in suppressing the activities of uveitis and some other systemic symptoms and maintaining the visual acuity in a certain number of patients where previous therapies with various immunosuppressive agents had failed to manage the ocular manifestation of the disease (Fujino et al. 1991; Mochizuki et al. 1993). A more recent report of FK 506 therapy in 41 patients with Behçet's disease showed improvement of ocular symptoms in a dose-dependent manner; 37.5% with an initial daily dose 0.05 mg/kg group, 60.0% with 0.1 mg/kg, 91.7% with 0.15 mg/kg and 78.6% with 0.2 mg/kg. The final improvement rate was 76.5% (Sakane et al. 1995).

Various adverse side effects were observed such as renal impairment, neurologic symptoms, gastrointestinal symptoms, hyperglycemia, hypomagnesemia and hyperkalemia. However, the majority of side effects disappeared or were improved after dose reduction or withdrawal from FK506 therapy (Sakane et al. 1995). The appropriate dosage of FK506 was between 0.10 and 0.15 mg/kg/day based on the efficacy and side effects (Mochizuki et al. 1993).

FK506 can be one candidate for therapy in Behçet's disease, but careful attention to its adverse effects is very important.

Cyclosporine. Cyclosporine is thought to work by blocking the synthesis and/or release of interleukin 1 from macrophages and interleukin 2 from helper T cells (Bunjes et al. 1981). There have been several reports of the effectiveness of cyclosporine in the treatment of Behçet's disease via its immunomodulatory effects. In 16 patients affected by the complete type of Behçet's disease, 5mg/kg/day of cyclosporine showed a marked improvement of symptoms after 3 months of therapy. Within 6-to-12 months of treatment, 14 of the 16 patients obtained
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a complete clinical remission (Pacor et al. 1994). It was effective especially in ocular manifestation of Behçet's disease (Atmaca and Batioglu, 1994; Sajjadi et al. 1994), and also effective in mucocutaneous symptoms including genital ulceration, thrombophlebitis, erythema nodosum-like lesions and acneiform lesions (Avci et al. 1997). Side effects consist of hirsutism, mild hyperbilirubinemia, nausea, hypertension, and mild urea retention (Müftüoglu et al. 1987). These side effects respond promptly to a reduction in the cyclosporine dose. An initial dose of 5mg/kg/day cyclosporin A is used in the systemic medical treatment of ocular Behçet's disease. Cyclosporin A can be continued at this low dosage for an unspecified time (Atmaca and Batioglu, 1994).

Interferon-alpha 2. Interferons, which possess antiviral, immunomodulatory, anti-proliferative, and antitumoral properties, have been tried in Behçet's disease (Durand et al. 1993; Alpsoy et al. 1994). It was found to be effective for posterior uveitis refractory to corticosteroid and cyclosporin A therapies and arthritis (Sanchez Roman et al. 1996; Kotter et al. 1996). It was also shown to reduce significantly the number, severity, duration and frequency in mucocutaneous lesions of Behçet's disease (Zouboulis et al. 1993; Azizlerli et al. 1996). Interferon alfa-2a can be administered subcutaneously at a dose of 3-18 million IU/day, three times per week (Alpsoy et al. 1994; Azizlerli et al. 1996). Side effects during interferon alfa-2a treatment included depression, thyroid changes, flu-like symptoms, increase of temperature, fatigue, myalgia, hypotension and diarrhea. Adverse reactions were generally mild and well tolerated (Zouboulis et al. 1993; Sanchez Roman et al. 1996).

Levamisole. Levamisole was found to be useful in ameliorating oral, genital, ocular, neurologic and gastro-intestinal involvement in Behçet's disease (de Merieux et al. 1981; Lavery and Pinkerton, 1985).

Although the exact mechanism of action of levamisole is not known, levamisole is thought to have effects on cellular immunity probably by influencing T cells and to augment cell-mediated immune responses (Lehner, 1977).

Levamisole is given at a dosage of 50mg three times daily for two days a week (James, 1979).

An important side effect of levamisole is neutropenia, while other less serious complications include flu-like symptoms, skin rash, and urticaria (Lehner, 1977).

Thalidomide. Thalidomide (α-pthalimido glutarimide) was first manufactured in 1954 and found to have excellent sedating properties. In 1956 it was introduced to the German market under the name Contergan (Mellin and Katzenstein, 1962; Allen, 1986). In spite of its efficacy as a hypnotic, thalidomide was withdrawn on November 27, 1961 because of the serious side effect of its teratogenicity (Mellin and Katzenstein, 1962). In 1965, Sheskin reported that thalidomide had a beneficial effect on erythema nodosum leprosum, and successful treatment in many other conditions have been subsequently reported (Allen, 1986; Larsson, 1990). Thalidomide was first reported as being of benefit in aphthous ulceration in 1979 by Mascaro et al. In previously reported cases, thalidomide was found to be of value in treating the variable symptoms of Behçet's disease such as mucocutaneous lesions, arthritic symptom, and colitis etc. (Saylan and Saltik, 1982; Allen, 1986; Hamza, 1986; Jorizzo et al. 1986; Jenkins et al. 1989; Larsson, 1990; Postema et al. 1996).

The mode of action of thalidomide in Behçet's disease is still unclear. The speed of response suggests that thalidomide is acting in an antiinflammatory or immunomodulatory capacity (Allen, 1986).

Thalidomide is introduced in a dose of 200-400 mg/day. Nerve conduction studies are undertaken before treatment starts and at 3-monthly intervals while it continues (Allen, 1986).

In 1994, Ochonisky et al. reported that the incidence of thalidomide neuropathy may be between 21% and 50%.

The occurrence of the neuropathy did not appear to be related to the daily dose or to the duration of treatment, and was shown to be irreversible in some cases.

When thalidomide therapy is considered, extremely careful preselection and monitoring of patients must be followed because of the known risks of teratogenicity and peripheral neuropathy.

Other side effects of thalidomide include endocrine effect, drowsiness, dizziness, changes of mood, constipation, and xerostomia (Tseng et al. 1996).

Zinc Sulfate. Zinc has been shown to exert an
influence on most aspects of the host immune response. Previous reports (Michalson et al. 1977; Beach et al. 1982; Berne et al. 1985; Norris, 1985) about modulation of autoimmune disease by zinc depletion continue to stimulate our interest in the role of zinc in cutaneous inflammation. Only a few reports suggest the association of zinc in the pathogenesis of Behçet’s disease (Cengiz and Gürkaynak, 1986). Through the measurement of serum zinc levels in patients with Behçet’s disease, we found that some patients showed a low level of serum zinc. In these patients, we experienced a good therapeutic result with the oral administration of zinc sulfate alone (Bang et al. 1991). Zinc sulfate, 100 mg in a capsule two or three times daily, was given by oral administration.

In our investigation, the patients with Behçet’s disease who had a low serum zinc level (≤ 70 μg/dl) showed a significant increase of T8 cells and a decrease of the T4/T8 ratio in comparison with normal controls. Also we found that serum zinc had an inhibitory effect on natural killer(NK) cell activity but did not affect antibody-dependent cellular cytotoxicity (ADCC) in Behçet’s disease patients (Chung et al. 1994). Zinc sulfate is considered to be a good supportive agent which can influence the immune status of patients when given as an additive to the combination-agent regimen.

Other Systemic Therapies. Effectiveness has been noted in various studies using subcutaneous injections of transfer factor derived from the lymphocytes of healthy people (Bernhard and Heim, 1974; Wolf et al. 1977).

Ethylestrenol and phenformin have been used to treat patients with thrombophlebitis (Cunliffe and Menon, 1969). Streptokinase and stanozolol have also been used (Newland and Cunliffe et al. 1977; Wood, 1978). These drugs may have been acting by decreasing platelet adhesiveness or by modifying fibrinolysis in the tissues.

The oral Sabin polio vaccine has been used in Israel with encouraging results as a treatment of Behçet’s disease (Fischel et al. 1980). The mode of action of the vaccine is yet to be elucidated.

The use of chloroquine or hydroxychloroquine was helpful in 5 patients with Behçet’s disease (O’Duffy, 1978-79).

Nonsteroidal antiinflammatory drugs such as aspirin and indomethacin have helped in select circumstances (Scarlett et al. 1979). Indomethacin was effective in treating arthritic symptoms in Behçet’s disease (Simsek et al. 1991).

Low-dose oral methotrexate, 7.5-to-20 mg per week, is effective for resistant mucocutaneous disease, but its use should be restricted to carefully selected patients (Jorizzo et al. 1991).

Promising results have been achieved with dapsone, 100 mg daily (Sharquie, 1984). Dapsone is thought to work by inhibiting the chemotaxis of polymorphonuclear leukocytes and by preventing auto-oxidative tissue injury (Anderson et al. 1981). Because dapsone can cause a hemolytic anemia and methemoglobinemia that can be severe in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a G6PD level should be checked before therapy. Sulfasalazine, 2-to-4g/day, is reported as being beneficial in gastrointestinal involvement of Behçet’s disease (Yazici and Barnes, 1991).

Minocycline hydrochloride showed not only clinically to reduce some symptoms of Behçet’s disease patients but also to regulate inflammatory cytokines produced from peripheral blood mononuclear cells of Behçet’s disease patients when they were stimulated with streptococcal antigen in vitro (Oyama et al. 1996).

There have also been reports on the efficacy of acyclovir in the treatment of recurrent aphthous stomatitis or Behçet’s disease (Resegotti and Pistone, 1984; Dürhersen et al. 1986; Pedersen, 1992).

DNCB sensitization itself may have therapeutic effects in selected cases who show decreased cell-mediated immunity. Such immunologic effects can be augmented by the combination treatment of levamisole.

Surgical therapy

In serious conditions such as gastrointestinal perforation, enterocutaneous fistula formations, spontaneous arterial aneurysm formation, thrombotic obstruction in large caliber vessels, or cardiac involvement etc., then surgical treatment may be the only possible remedy.

It is very important to determine the proper timing.
for surgical treatment. Delayed wound healing or inflammation at operation sites which may be related with pathergy reaction must be considered in patients with Behçet's disease who have undergone surgery. Therefore intensive postoperative care should be followed.

CONCLUSION

We suggest that therapeutic agents be selected only after thorough evaluation of the immune state of each patient by using various tests and determining any aggravating or provoking factors (Bang, 1992). Our therapeutic principles are illustrated in Fig. 1.

In general, combination-agent regimens are more effective than single-agent regimens. In our clinical experience, colchicine proved to be an effective drug showing relatively fewer side effects during long-term use. Zinc is considered to be a good supportive agent which can influence the immune status of patients when given as an additive in combination-agent regimens (Bang et al. 1991).

Except for the acute state of Behçet's disease, corticosteroids should be considered the last line of therapy.

Our investigation also emphasizes that not all patients require cyclosporine or other strong immunosuppressive agents.

Because Behçet's disease has shown a clinical course of chronic recurrence even under treatment, a treatment modality with minimal side effects during long-term use should be chosen.

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