Clin Exp Med (2004) 3:10–20
DOI 10.1007/s10238-004-0033-4

REVIEW

M. Suzuki Kurokawa • N. Suzuki

Behcet's disease

Received: 1 September 2003 / Accepted: 23 October 2003

Abstract Behcet's disease (BD) is a systemic disorder of recurrent acute inflammation, characterized by major symptoms of oral aphthous ulcers, uveitis, skin lesions and genital ulcers. Involvement of intestines, vessels, and central nervous system (CNS) sometimes leads to a poor prognosis. Patients with BD are known to distribute along the ancient Silk Road. The incidence is relatively higher from eastern Asia to the Mediterranean area as roughly 1–10 patients in 10,000 people, whereas only 1–2 patients in 1,000,000 people in UK and North America. Although etiology of the disease is still unknown, high prevalence of HLA-B51, increased expression of heat shock protein 60 and Th1 dominant immune responses in the patients are considered important in its pathogenesis. Non-infectious neutrophil activation and infection with *Streptococcus sanguis* and herpes simplex virus would also be associated. Because BD lacks any pathognomonic symptoms and laboratory findings, the diagnosis relies largely upon the criteria proposed by the International Study Group for Behcet's disease in 1990. In Japan, the diagnosis was also made according to the Japanese criteria revised in 1987. Recently, the Behcet's Disease Research Committee of Japan again revised the Japanese criteria in 2003 to avoid overdiagnosis. The new Japanese criteria are introduced in this review. Differential diagnosis excluding Sweet's disease, pemphigus, erythema nodosum and Crohn's disease is important, and positive laboratory data for pathergy test, prick test for dead Streptococci and HLA-B51 are emphasized to make appropriate diagnosis in these criteria. Pathological findings of the disease-affected site such as erythematous nodosum is also stressed. Treatment for the disease has been chosen according to the clinical symptoms. Non-steroidal anti-inflammatory drugs, immunosuppressants, corticosteroids and colchicine are basically introduced. Recently, effects of interferon-α/β, anti-tumor necrosis factor antibody and thalidomide are encouraging, specifically in treatment for the cases with poor prognosis including eye, intestine, vessel and CNS involvement. Low dose weekly administration of methotraxate looks effective for the cases with CNS involvement. Further studies for elucidation of the etiology, improvement of the diagnostic criteria and development of new therapy are needed to conquer the disease.

Key words Heat shock protein • Auto-reactivity • Tumor necrosis factor • Interferon • Diagnostic criteria

M. Suzuki Kurokawa • N. Suzuki (✉)
Departments of Immunology and Medicine,
St. Marianna University School of Medicine,
2-16-1, Sugao, Miyamae-ku, Kawasaki,
Kanagawa 216-8511, Japan
e-mail: n3suzuki@marianna-u.ac.jp
Tel.: +81-44-977-8111
Fax: +81-44-975-3315

Introduction

Behcet's disease (BD) is a systemic disorder characterized by recurrent attacks of acute inflammation [1, 2]. The symptoms include oral aphthous ulcers, uveitis, skin lesions, and genital ulceration. Involvement of the intestines, vessels, and central nervous system (CNS) is less frequent. However, it sometimes leads to a poor prognosis. Although the etiology of the disease is still unknown, various environmental and genetic factors are implicated in its pathogenesis. Recent advances in the pathogenesis, diagnosis, and therapy are discussed in this review.

Epidemiology

It is well known that patients with BD are distributed along the ancient Silk Road from eastern Asia to the Mediterranean area [1]. Interestingly, those who have HLA-B5 distribute among the same areas. This suggests a contribution of genetic background to the pathogenesis of BD. In contrast, there are few BD patients in other European countries and in North America. The incidence is roughly 1 in 1,000 in Turkey, which has the highest incidence, and 1 in 10,000 in Japan, Korea, Iran, and Saudi Arabia, and 1 in 500,000 in UK and 1 in 1,000,000 in North America [1, 3]. It is noteworthy that the incidence in Turkish descents in Berlin (1 in 5,000) is lower than in Turkey but is much higher than in German natives (1 in 200,000) [3]. The incidence in American people of Japanese descent is also lower than that in Japan [3]. Therefore, not only genetic factors but also environmental factors are considered important in the occurrence of BD.

The number of BD patients markedly increased after World War II in Japan. Young patients, especially young male patients with visual loss, particulary increased. BD frequently occurs in the thirties and is more prevalent in men than in women. There have been some changes in the epidemiology recently. The number of female patients is increasing and the male, female ratio has become nearly 1:1. The number of patients with severe eye involvement has to decreased recently in Japan. The number patients visiting ophthalmology departments has decreased recently [4]. The number of female patients with mild disease is increasing. To investigate the changes, the BD Research Committee of Japan planned a nation wide epidemiological study last year. A similar tendency for milder forms of the disease and a decrease in the number of patients with ocular lesions was reported in Iran [4].

Pathogenesis

Up to the 1980s, BD was considered an aseptic inflammatory disease. In spite of the severe infiltration of neutrophils in biopsy specimens of the disease-affected sites such as oral aphthous ulcers, erythema nodosum, and pathergy reaction, bacteria were rarely found on histological examination. Therefore, non-infectious neutrophil activation was suspected as an etiology of this disease. In accordance with this hypothesis, colchicine, an inhibitor of neutrophil activation, was found to be effective for treating patients with BD (controversy exists as to this point).

Recent advances have forced us to reconsider viral and bacterial infections as etiological factors. A high incidence of tonsillitis and dental caries in BD and sensitization of BD lymphocytes by streptococcal antigens suggest involvement of streptococci in the pathogenesis [5, 6]. A high serum antibody titer against *Streptococcus sanguis* in BD patients was reported [7]. Inoculation of *S. sanguis* into IQI mice induced iridocyclitis [8]. Autoimmune responses to self heat shock protein (HSP) in patients suggest that bacterial HSP may be involved in triggering the disease in individuals with genetic predisposition because of their high amino acid sequence homology [9, 10]. Herpes simplex virus (HSV) is possibly associated with the pathogenesis. An increase in IgG anti-HSV-1 antibodies in sera was reported during the active phase of BD [11]. When HSV DNA in saliva was detected by polymerase chain reaction the frequency of positive individuals was significantly higher in the BD group than healthy controls [12]. Inoculation of HSV into ICR mice induced BD-like symptoms, including mucocutaneous ulcers, eye syndromes, and arthritis [13]. Although BD is not a classical infectious disease, it is possible that microbial infection is involved in the pathogenesis.

HLA-B51

A high prevalence of HLA-B51 in BD patients, especially those living in areas along the Silk Road, has been reported. However, it is not clear whether HLA-B51 itself is a susceptiblity gene or not. The strong association might be due to linkage disequilibrium with another gene residing within the locus [14, 15]. Several studies have analyzed linkage between HLA-B51 or other nearby genes and the disease and have found the strongest linkage with HLA-B51 itself; association of other genes, including MICA, was secondary to the strong linkage disequilibrium with HLA-B51 [16–18].

The genotype of HLA-B51 has been analyzed in BD patients in various countries [19–25]; 21 alleles were identified for HLA-B51 molecules, designated as HLA-B*5101 to B*5121. Studies in ten countries along the Silk Road disclosed that 26%–77% of patients were HLA-B51 positive. Genotype analyses showed that most patients possessed HLA-B*5101 (62%–98% in each country) and to a lesser extent HLA-B*5108 (10%–30%). Collectively, BD patients globally possess the HLA-B51 molecule, suggesting that this is generally important for the pathogenesis.

Neutrophil hyperfunction was a characteristic of BD. fMLP-induced superoxide production by neutrophils was significantly enhanced in HLA-B51-positive individuals, regardless of the presence or the absence of BD, compared with HLA-B51-negative individuals [26]. A similar result was obtained in the study comparing HLA-B51 and HLA-B35 transgenic and non-transgenic mice, suggesting that the excessive function of neutrophils in BD is associated with the presence of HLA-B51.

Heat shock protein

Human mitochondrial HSP is highly homologous with microbial HSP and provokes proliferation of autologous T cells in patients with BD. The human 60-kilodaltol HSP-

derived peptides were capable of inducing uveitis in rats [27]. We have reported that the human HSP60 peptide, 336–351, yielded T cell proliferation in Japanese BD patients, but not in patients with rheumatoid arthritis or in normal subjects [28]. The proliferation by this peptide was significantly associated with the presence of ocular lesions of BD. Stimulation by the HSP peptide induced antigen-specific T cell responses, and mRNA of interleukin (IL)-8, tumor necrosis factor (TNF)-α, and TNF-β was expressed in peripheral blood mononuclear cells (PBMC) of patients. The peptide or HSP itself may be responsible for provoking inflammatory reactions in the disease. BD patients in Turkey were similarly tested for T cell responses to mycobacterial HSP peptides or to similar human HSP peptides [29]. Cell populations responding to the peptides and stimulation indexes were significantly higher in the BD compared with other inflammatory diseases and the healthy group. We and others found increased expression of HSP 60/65 in BD mucocutaneous lesions [30]. This suggests a contribution of HSP to the immunopathogenesis of BD.

Th1/Th2 responses

The cytokine profile of BD is skewed towards the Th1-type immune responses, especially in active patients [31–33]. Serum IL-12 levels correlate with disease activity and higher levels of soluble TNFR-75 were present in active BD [31]. Th1 cells that express interferon (IFN)-γ and CD40L upon in vitro stimulation increased in number in active BD [32]. Increased production of IL-2 and IFN-γ in BD patients was reported, where the IFN-γ-producing cells (Th1 cells) and serum IL-12 levels paralleled progression of BD [33].

Overproduction of Th2 cytokines in BD patients was also reported [31, 32, 34]. One report suggests an increase of both Th1cytokines (IFN-γ and IL-12) and Th2 cytokines (IL-4, IL-6, and IL-10) in BD patients [32]. It is suggested that IFN-γ, IL-17, and IL-18 were extremely high in active BD and IL-6 and IL-10 were also high in active BD. Another report suggests that BD patients produced higher levels of IL-4, IL-10, and IL-13 (Th2), but a, normal level of IL-2 (Th1) and highly deficient IFN-γ and IL-12 (Th1).

We have investigated the cytokine production of BD patients. PBMC produced extremely large amounts of IFN-γ in patients with BD (manuscript in preparation). Th1 cytokines (IFN-γ, TNFα, and IL-12) were detected on skin biopsy during the active phase. Th2 cytokines (IL-4, IL-10, and transforming growth factor-β) were detected when the lesions were subsiding. The Th1 to Th2 shift was quite prompt. Furthermore, we found that protein expression of Txk, a Th1-specific transcription factor essential for IFN-γ production, was up-regulated in BD, and the down-regulation of Txk occurred within a couple of hours of Th2 cytokine exposure. Thus, Th2 cytokine expression may be involved in attenuation of the symptoms of BD. In accordance with our findings, it was reported that depletion of macrophages suppressed BD-like symptoms and the suppression was correlated with IL-4 expression in splenocytes in the BD model of ICR mice [35]. Taken together, it is possible that the Th1 shift first occurred in BD via Txk overexpression in CD4+ T cells and Th2 cytokine production was modified to attenuate the inflammatory conditions. This prompt shift (or switch) from Th1 to Th2 cytokine production may make the interpretation of cytokine contribution to the pathogenesis of BD difficult.

Diagnosis

BD lacks any pathognomonic symptoms or laboratory findings. Therefore, the diagnosis relies upon the criteria proposed by the International Study Group for Behcet's disease in 1990 [36]. In Japan, the diagnosis has also been made according to the criteria revised in 1987 by the Behcet's Disease Research Committee of Japan. Major characteristics of the 1987 Japanese criteria were mucocutaneous and ocular symptoms and the criteria were simplified for the diagnosis. It was found, however, that the number of newly diagnosed patients has rapidly increased [37]. For example, there were 11,890 patients in 1989; this increased to 16,640 in 1998. After careful differential diagnosis by experts, it became clear that a considerable proportion of patients had been overdiagnosed as having BD [37]. Representative cases of the overdiagnosis include Sweet's disease, pemphigus, erythema nodosum, and Crohn disease. A similar tendency for overdiagnosis may be present when we use the international criteria.

To improve accuracy of diagnosis, the Behcet's Disease Research Committee of Japan has again revised the criteria. We have translated the revised criteria for diagnosis in 2003 (Table 1), activity (Table 2) and severity (Table 3) into English. The major characteristics of the revised criteria 2003 are as follows.

1. The main symptoms include recurrent aphthous ulcers on the oral mucosa, skin lesions, ocular lesions and genital ulcers.
2. Additional symptoms are defined as: arthritis, epididymitis, gastrointestinal lesions, vascular lesions, and CNS lesions.
3. The disease types are defined as: complete type, incomplete types, BD suspected, and special lesions. A patient having some of the main symptoms, but not fulfilling the criteria for the incomplete type, is categorized as "BD suspected".
4. The revised criteria employ clinical and laboratory data for the diagnosis. They include pathergy test and prick test for dead *Streptococcus*. HLA-B51 and pathological findings of erythema nodosum are also important.
5. The revised criteria list major diseases for the differential diagnosis.

Detailed information on BD itself and diseases in the differential diagnosis were introduced to avoid overdiagnosis.

Table 1 Revised diagnostic criteria proposed by the Behcet's Disease (BD) Research Committee of Japan in 2003. (*ESR*, erythrocyte sedimentation rate, *CRP* C-reactive protein)

- Main points
  - Main symptoms
    - Recurrent aphthous ulcers on oral mucosa
    - Skin lesions
      - a. Skin lesion with erythema nodosum
      - b. Subcutaneous thrombophlebitis
      - c. Follicular papules, acneform papules
        - cf.) Skin hypersensitivity
    - Ocular lesions
      - a. Iridocyclitis
      - b. Posterior-uveitis (retinochoroiditis)
      - c. If the patients have the following eye symptoms after (a) and (b), diagnose as BD lesions in accordance with (a) and (b)
        - Posterior adhesion of iris, pigmentation on lens, retinochoroid atrophy, atrophy of optic nerve, complicated cataract, secondary glaucoma, leakage of bulbus oculi
    - Genital ulcers
  - Additional symptoms
    - Arthritis without deformity or sclerosis
    - Epididymitis
    - Gastrointestinal lesion represented by ileocecal ulceration
    - Vascular lesions
    - Central nervous system lesions moderate or severe
  - Criteria for diagnosis of disease types
    - Complete type
      - The four main symptoms appeared during the clinical course
    - Incomplete types
      - Three of the main four symptoms, or two main symptoms and two additional symptoms, appeared during the clinical course
      - Typical ocular lesion and another main symptom, or two additional symptoms appeared during the clinical course
    - BD suspected
      - Although some main symptoms appear, the case does not meet the criteria for the incomplete type
      - Typical additional symptom is recurrent or becomes more severe
    - Special lesions
      - Gastrointestinal lesions – presence of abdominal pain and occult blood should be confirmed
      - Vascular lesions – vasculitis of aorta, artery, large veins, or small veins should be differentially diagnosed
      - Neuronal lesions – presence of headache, paresis, lesions of brain and spinal cord, mental symptoms, and other symptoms should be confirmed
- Clinical laboratory data
- Clinical laboratory data contributing to the diagnosis (not essential)
  - Negative or positive pathergy test (use needles of diameter is 18–22 G)
  - Negative or positive prick test for vaccine for streptococci
    - Hypersensitivity to streptococci
    - Because most BD patients show hypersensitivity to streptococci present in oral mucosa, such as *Streptococcus sanguis*, a severe response of erythema is seen after prick test for antigen from dead streptococci (diameter of the needles for the prick test should be 26G).
  - Inflammatory responses
    - Increase of ESR, CRP positive, neutrophilia in peripheral blood, increase of complement activity
  - Positive for HLA-B51 (B5)
  - Pathological findings
    - Skin lesion similar with erythema nodosum in acute phase is septal adipose inflammation infiltrated by neutrophils and mononuclear cells. Infiltration by mononuclear cells is the main finding and histology shows lymphocytic vasculitis. Presence or absence of necrotic vasculitis should be confirmed, since its presence suggests systemic vasculitis and is complicated in a considerable number of patients
- Additional points
  - Non-typical symptoms should not be diagnosed as BD both in the case of main symptoms and additional symptoms
  - As for the main symptoms of skin lesions, one of the criteria (a) to (c) is enough for the diagnosis if the lesion occurs frequently. In the case of ocular symptoms either of (a) or (b) is enough for the diagnosis

Cont. →

Cont. Table 1

Ocular symptoms

Posterior adhesion of iris, pigmentation on lens, retinochoroid atrophy, atrophy of optic nerve, complicated cataract, secondary glaucoma, and leakage of bulbus oculi, all of which occur after iridocyclitis and posterior uveitis, can be diagnosed as the main symptom of ocular lesion. If the origin of these lesions is unconfirmed; however, they should be defined as additional findings for the diagnosis

Additional symptoms

One should pay attention to the presence of many diseases that should be differentially diagnosed from BD (refer to the criterion for differential diagnosis). If the differential diagnosis is not sufficient, the symptoms should be defined as additional findings for the diagnosis

A case lacking any inflammatory findings is questionable as BD. Serum complement activity is increased in most cases of BD, however, one should suspect collagen diseases if the case is complicated by prominent hypergamma globulinemia or positive anti-nuclear antibody

Major diseases that should be differentially diagnosed

Diseases involving mucosa, skin, and eyes

Erythema multiforme exsudativum, acute drug poisoning, Reiter disease

Diseases that show one of the main symptoms of BD

Oral/mucosal legions: chronic recurrent aphthous ulceration, Lipschutz's genital ulcers

Skin legions: folliculitis abscedens, acne vulgaris, erythema nodosum, movable venous thrombosis, single venous thrombosis, Sweet disease

Ocular symptoms: metastatic intraocular inflammation, septic retinitis, leptospirosis, sarcoidosis, ankylosing spondylitis, central retinitis, juvenile recurrent vitreoretinal hemorrhage, retinal venous thrombosis

Similar diseases with main and/or additional symptoms of BD

Oral/mucosal legions: herpes labialis, stomatitis (herpes simplex type I)

Genital ulcers: infection of herpes virus type II

Skin lesions like erythema nodosum: erythema nodosum, Bazin's erythema induratum, sarcoidosis, Sweet disease

Arthritic symptoms: collagen diseases such as rheumatoid arthritis, systemic erythematosus and systemic sclerosis, gout, psoriatic arthritis

Gastrointestinal symptoms: acute appendicitis, Crohn disease, ulcerative colitis, acute/chronic pancreatitis

Epididymitis: tuberculosis

Vascular symptoms: Takayasu disease, Buerger disease, arteriosclerotic aneurysm, deep venous thrombosis

Central nervous symptoms: infectious/allergic meningitis, cerebritis and inflammation of spinal cord, systemic lupus erythematosus, brain/spinal cord tumors, vascular disorders, syphilis, multiple sclerosis, mental diseases, sarcoidosis

Table 2 Classification of phases of activity in BD proposed by the BD Research Committee of Japan in 2003

Active phase

One of the following symptoms is found: uveitis, subcutaneous venous thrombosis, skin lesion such as erythema nodosum, genital ulcers (those relating to the female sexual cycle should be excluded), arthralgia, intestinal ulceration, progressive central nervous system lesions, progressive vasculitis, and epididymitis

Inflammatory findings are also evident from clinical examination (including ophthalmological findings) and/or clinical laboratory findings (serum CRP, findings in cerebral fluid, findings by colonic fiberscopy, and others)

As for oral aphthous ulcers, skin/genital ulcers, and ocular symptoms, cases with a score of 2 or above are defined as BD in the active phase

Non-active phase

Cases excluded by the above definition for active phase

*1 Dosage up, change or addition of therapeutic reagents is generally required in the active phase

*2 As for cases with only oral aphthous ulcers or follicular papules, careful diagnosis is recommended taking into account other symptoms or past symptoms, since these symptoms are not good criteria for disease activity

*3 In cases of lesions in which attack is obvious, for example uveitis, active phase corresponds to the attack phase and the lesions continue for no longer than 2 weeks in general. However, if obvious inflammatory findings continue for more than 2 weeks, cases can be diagnosed as in the active phase at present

*4 One should consider that it is possible that cases in the inactive phase suddenly move into the active phase

*5 Stable phase (remission) is defined as the inactive phase with the activity index of 0 for more than 1 year

Activity index

Oral aphthous ulcers

Score 0: no ulcers

Cont. →

Cont. Table 2

Score 1: the symptom persisted for less than 2 weeks during the post 4 weeks
Score 2: the symptom persisted for 2 weeks or more than 2 weeks during the past 4 weeks
Score 3: the symptom was mostly present during the post 4 weeks

Skin lesions (skin lesions such as erythematic nodosum)
Score 0: no lesions
Score 1: the symptom persisted for less than 2 weeks the past 4 weeks
Score 2: the symptom persisted for 2 weeks or more than 2 weeks during the past 4 weeks
Score 3: the symptom was mostly present during the past 4 weeks

Ocular lesions (uveitis)
Score 0: no uveitis
Score 1: ocular attack (including inflammation of the opposite eye that serially occurred within a few days) occurred only once during the past 4 weeks
Score 2: the attack occurred twice during the past 4 weeks
Score 3: the attack occurred three times during the past 4 weeks

Other symptoms
Arthritis: arthralgia, swelling, walking difficulty, deformity, and others
Gastrointestinal symptoms: acute/chronic abdominal pain, melena, or occult blood
Epididymitis: pain, swelling
Vascular lesions: cardiac/aortic disorders, obstruction of middle vessels, obstruction of small vessels, thrombophlebitis, and others
Central nervous system lesions: headache, dizziness, paralysis, mental symptoms, and others
Other symptoms and complications

Table 3 Criteria for the severity of BD proposed by the BD Research Committee of Japan in 2003

Stage	Criteria
I	Main symptoms (oral aphthous ulcers, skin legions and genital ulcers) except ocular lesions are found
II	Iridocyclitis is found as an ocular symptom in addition to the stage I symptoms Arthritis and/or epididymitis is/are found in addition to the stage I symptoms
III	Cases with retinochoroiditis
IV	Cases with possible visual loss or retinochoroiditis with involvement of the other eye leading to visual loss Special disease types (intestinal-Behcet, vasculo-Behcet, or neuro-Behcet) with activity or severe sequelae
V	Special disease types of BD with risk for prognosis Cases of progressive neuro-Behcet of which intelligence is affected moderately or more severely
VI	Death (one should clarify the cause of the death, i.e., (a) the cause is based on the symptoms of BD, (b) based on complications, and others)

• As for stages I and II, cases are diagnosed as in stable phase (remission) if active phase lesions have not found for more than 1 year. If a disease state does not fulfill the criteria, however, cases are not diagnosed as in the stable phase
• Visual loss defined by summation of visual acuity on both sides is less than 0.12, or range of vision of both sides is less than 10°
• Uveitis, subcutaneous thrombophlebitis, erythema nodosum, genital ulcers (those related to the female sexual cycle should be excluded), arthralgia, intestinal ulcers, progressive central nervous system lesions, progressive vasculitis, or epididymitis is found and inflammatory findings are evident from clinical examination (including ophthalmological findings) and/or clinical laboratory tests (serum CRP, serum complement activity, findings in cerebral fluid, findings by colonic fiberscopy, and others)

This is very useful for the accurate diagnosis of BD. Those who are not familiar with this disease may find the differential diagnosis complicated. The HLA-B51 test was included because HLA-B51 is a critical factor. Hence, HLA typing is globally useful in all patients diagnosed or suspected of having BD.

Taken together, detailed examination and pathological findings described in the revised Japanese criteria 2003 are considered important for the diagnosis. The most critical point for the diagnosis is excluding other similar diseases. The revised Japanese criteria could be helpful for the differential diagnosis in other countries.

Therapy

The choice of treatment depends on the clinical manifestations [1, 38]. A combination of local and systemic therapy is generally given. Non-steroidal anti-inflammatory drugs, immunosuppressants, corticosteroids, and colchicine are

used. Treatments for ocular lesions require more-careful consideration than for mucocutaneous lesions [1]. In particular, CNS involvement and large-vessel vasculitis tend to have unsatisfactory outcomes. Colchicine is widely used in Japan and is effective in approximately half of the patients [38]. Cyclosporine A is effective in a half of the rest; however, it sometimes worsens neurological lesions. Therefore magnetic resonance imaging (MRI) of the CNS is recommended before administration. Although high-dose corticosteroids have been used for intestinal and CNS lesions, some patients were refractory to all treatments currently available. Novel therapeutic approaches may shed new light on treatments for refractory symptoms in BD.

Interferon-α

IFN-α shows anti-viral activity and restores the low natural killer cell activity in BD. Clinical studies have been conducted for more than 20 years suggesting the efficacy of IFN-α [39–47]. Although the targeted lesions were different in the studies, approximately 60%–100% of BD lesion entered remission by using IFN-α (Table 4). IFN-α is useful not only for mucocutaneous and ocular lesions but also for arthritis, vasculitis, and CNS lesions. Approximately half of the patients have continued their remission after termination of IFN-α. IFN-α reduced maintenance dosages of corticosteroid needed for most patients even after its termination. The remaining

Table 4 Results of novel therapies for BD (*IFN* interferon, *CNS* central nervous system, *I* total improvement, *TFN* tumor necrosis factor, *E* excluded, *N* no total improvement)

Study	No. of patients	Initial dosage	Improvement						
			Oral ulcers	Genital ulcers	Skin lesions	Ocular lesion	Arthritis	Vasculitis	CNS lesions
IFNα									
Hamuryudan et al. [39] (1993) (IFN-α2b) 3 times/week	20	5 x 10^6	*/20	*/17	*/14	–	**/9	–	–
Azizlerli et al. [40] (1996) (IFN-α2b) 3 times/week	18	3 x 10^6	15/18 (83%)	8/10 (80%)	10/16 (63%)	1/1 (100%)	–	–	–
O'Duffy et al. [41] (1998) (IFN-α2a) Daily	10	3 x 10^6	5/9 (56%)	4/4 (100%)	2/3 (67%)	–	3/6 (50%)	–	–
Georgiou et al. [42] (1998) (IFN-α2a) 3 times/week	12	6 x 10^6	9/12 (75%)	8/11 (73%)	6/9 (67%)	3/3 (100%)	–	1/1 (100%)	–
Boyvat et al. [43] (2000) (IFN-α2a) 3 times/week	20	9 x 10^6	15/18 (83%)	11/13 (85%)	9/12 (75%)	–	–	–	–
Wechsler et al. [44] (2000) (IFN-α2a) 3 times/week	8	3 x 10^6	–	–	–	8/8 (100%)	–	–	–
Demiroglu[a] et al. [45] (2000) (IFN-α2b) once/2 days	67	3 x 10^6	I/67	I/36	I/40	I/8	I/12	I/4	–
Hamuryudan[b] et al. [46] (2002) (IFN-α2b) 3 times/week	10	5 x 10^6	7/10 (70%)	7/9 (78%)	7/8–10	9/9 (100%)	–	–	–
Cairguneri et al. [47] (2003) (–) 3 times/week	29	5 x 10^6	–	–	–	13/17 (76%)	11/11 (100%)	9/10 (90%)	4/4 (100%)
anti-IFN									
Travis et al. [51] (2001)	infliximab 2	3–5 mg/kg	***/2	2/2	2/2	–	2/2	1/1	
Sfikakis et al. [52] (2001)	infliximab 5	5 mg/kg	2/2	–	5/5	–	1/1	–	
Aeberli et al. [53] (2002)	infliximab 2	3–5 mg/kg	–	–	–	1/1	–	–	

Cont. →

Cont. Table 4

Melikoglu[c] et al. [4] (2002)	etanercept 40	25 mg/ 2 weeks	I	–	I	–	I	–
Melikoglu[d] et al. [4] (2002)	etanercept 10	25 mg/ 2 weeks	–	–	–	I	–	–
Thalidomide								
Saylan**** et al. [56] (1982)	22	400 mg/day	I/22	I/16	–	N/3	–	–
Hamza***** et al. [57] (1986)	30	100–300 mg/day	20/27 (74%)	20/25 (80%)	4/4 (100%)	3/11 (27%)	13/14 (93%)	–
Jorizzo[f] et al. [58] (1986)	4	200 mg/day	2/2 (100%)	2/2 (100%)	–	–	2/2 (100%)	1/2 (50%)
Grinspan[e] et al. [59] (1989)	100	100–300 mg/day	34/100 (34%)	–	–	–	–	–
Gardner-Medwin[g] et al. [60] (1994)	23	100–200 mg/day	– (83%)	–	–	–	–	
Hamu-Ryudan[h] et al. [61] (1998)	96	100 mg/day 300 mg/day	I/28 I/26	I/12 I/8	I I	I/14 I/14	– –	E E
Kari[i] et al. [62] (2001)	5	1–7mg/kg per week	5/5 (100%)	5/5 (100%)	–	1/1 (100%)	–	–

*Mean number of mucocutaneus lesions showed a decrease but it was not significant
**Mean number of arthritis attacks and their mean duration were significantly reduced
***One case was reported to resolve
****Patients with oral and genital lesions but without ocular involvement recovered from the ulcers almost immediately. Thalidomide was not effective in treating severe ocular attacks, however, it was partially useful in some patients
*****Number of patients who showed complete recovery was shown. Including partial recovery, 26/27 (96%), 24/25 (96%), 6/11 (55%), and 14/14 (100%) patients with oral ulcers, genital ulcers, ocular lesions, and arthritis were improved, respectively
[a] IFN-α was used in combination with colchicine and benzathine penicillin in this study. All types of mucocutaneous lesions were less frequent in the IFN group than in patients without IFN (colchicine and benzathine penicillin group)
[b] IFN-α was used in combination with azathioprine in this study. Seven patients were completely free from mucocutaneous lesions during treatment. Nine patients with ocular lesions were re-evaluated after the IFN therapy
[c] Number of patients who received placebo was included. Significant beneficial effects were seen in the indicated lesions
[d] Combined treatment with corticosteroids, azathioprine, and cyclosporine A was given before this trial. Etanercept was added to the previous treatment and showed a beneficial effect in maintaining visual acuity
[e] The remaining 66 patients showed not complete but marked improvement. Thus, all the patients with orogenital ulcers (100%) nearly recovered
[f] Since 2 patients were withdrawn from the study, the remaining 2 patients were evaluated. At least 1 patient recovered from nervous lesions
[g] Patients with oral or genital ulcers were treated
[h] Patients were divided into three groups and outcomes of 32 patients who received thalidomide 100 mg/day, 31 who received thalidomide 300 mg/day, and 32 who received placebo were evaluated. The suppressive effect of thalidomide at both dosages was significant at 4 weeks for oral ulcers and at 8 weeks for genital ulcers and follicular lesions. Patients from both thalidomide groups had significantly fewer eye attacks and milder deterioration in visual acuity in both eyes than did patients in the placebo group
[i] Thalidomide was given to children with BD whose ages were 7–16 years at the start

patients, however, experienced recurrence. Zouboulis and Orfanas [48] reviewed 22 original reports of 144 BD patients treated with IFN-α. Mucocutaneous manifestations, uveitis, and arthropathy/arthritis had a partial or complete response, IFN-α-2a was more effective than IFN-α-2b, and majority of patients experienced recurrences. They recommended a 3-month high-dose regimen followed by a low maintenance dose.

Common side effects include flu-like symptoms, leukocytopenia, liver damage, and alopecia [39–42, 44–47]. Prospective multicenter double-blinded study of IFN-α therapy is awaited to confirm the effect, especially on vascular and CNS lesions.

Tumor necrosis factor-α

Serum concentrations of TNF and soluble TNF receptors were increased in BD patients. TNF is thought to play a key role in rheumatoid arthritis and Crohn disease, and a thera-

peutic effect of anti-TNF has been reported [49, 50]. Several groups have reported success in the treatment of BD with TNF-α blockade, including infliximab (anti-TNF monoclonal antibody) and etanercept (soluble TNF receptor) [4, 51–53]. The effect of TNF-α blockade reported in patients with BD was striking (Table 4). Infliximab was effective for treating gastrointestinal ulceration and relapsing panuveitis [51, 52]. Most lesions refractory to conventional treatments entered remission within a few weeks of TNF-α blockade [53]. After termination of anti-TNF therapy, however, they recurred within several months in most cases.

Adverse effects of anti-TNF agents in BD were not negligible. These include serious infection, including tuberculosis, autoantibody production, and other respiratory, gastrointestinal, and dermatological symptoms [53, 54]. Nonetheless, anti-TNF agents are promising in those with symptoms refractory to conventional treatments.

Thalidomide

Thalidomide has immunomodulatory and anti-inflammatory properties. It reduces the activity of the inflammatory cytokine TNF-α by accelerating the degradation of its mRNA [55]. It was also reported to inhibit angiogenesis. The effect of thalidomide seemed to be rather restricted [56–62]. It induced nearly all the genital ulcers and arthritis to enter complete remission or at least partial remission. However, effects on ocular and skin lesions were inconsistent, and depended on the studies [56, 57, 61]. Rather, thalidomide sometimes brought about harmful effects on skin lesions [56, 61].

The effect of thalidomide continued during the treatment but diminished rapidly after its termination. Nervous system side effects were prompt such as somnolence, polyneuropathy, impairment of libido, dizziness, and sleeplessness [56, 57, 59–61]. Other adverse events were exaggerated appetite, fatigue, constipation, xerostomia, headache, weight gain, skin rash, edema, and sweating [56–59, 61].

Female patients must be warned of teratogenesis. In summary, thalidomide seems to be worth trying in those with severe and recurrent mucocutaneous lesions.

Methotrexate for CNS lesions

CNS lesions constitute one of the most-serious symptoms. CNS lesions are usually treated with high-dose corticosteroids. However, many patients were refractory to the corticosteroid therapy. Methotraxate (MTX), which inhibits folic acid metabolism and then decreases synthesis of nucleic acids, has been used to treat cutaneous neutrophilic vascular reactions and ocular lesions of BD [63, 64]. MTX was applied to patients with progressive neuro-BD (progressive dementia or psychosis) by low-dose weekly administration (7.5–12.5 mg/week) for 12 months [65]. MTX reduced the cerebrospinal fluid IL-6 levels significantly, whereas intelligence quotients and findings on MRI examination were comparable at the end of the therapy. Six months after the discontinuation of MTX, the neuropsychological manifestations exacerbated and cerebrospinal fluid IL-6 was elevated. As a side effect, liver dysfunction, which returns to normal on reducing the MTX dosage, is rather common. In summary, low-dose weekly MTX therapy may be a choice for treating steroid refractory neuro-BD.

Conclusions

Although many studies have investigated the pathogenesis of BD, it remains unknown. We describe revised diagnostic criteria in Japan and novel therapies. Further studies are needed to clarify the etiology, improve the specificity of diagnosis, and develop new therapeutic strategies.

References

1. Sakane T, Takeno M, Suzuki N, Inaba G (1999) Current concepts: Behcet's disease. N Engl J Med 341:1284–1291
2. Barnes CG, Yazici H (1999) Behcet's syndrome. Rheumatology 38:734–736
3. Zouboulis CC, Kotter I, Djawari D, Kirch W, Kohl PK, Ochsendorf FR, Keitel W, Stadler R, Wollina U, Proksch E, Sohnchen R, Weber H, Gollnick HP, Holzle E, Fritz K, Licht T, Orfanos CE (1997) Epidemiological features of Adamantiades-Behcet's disease in Germany and in Europe. Yonsei Med J 38:411–422
4. Fresko I (2002) Highlights of the 10th International Congress on Behcet's Disease. Clin Exp Rheumatol 20 [Suppl 26]:S59–S64
5. Aoki K, Ohno S (1972) Studies on the constitution and past history of patients with Behcet's disease. Acta Soc Ophthalmol Jpn 76:1608–1612
6. Kaneko F, Takahashi Y, Muramatsu Y, Miura Y (1985) Immunological studies on aphthous ulcer and erythema nodosum-like eruptions in Behcet's disease. Br J Dermatol 113:303–312
7. Yokota K, Hayashi S, Fujii N, Yoshikawa K, Kotake S, Isogai E, Ohno S, Araki Y, Oguma K (1992) Antibody response to oral streptococci in Behcet's disease. Microbiol Immunol 36:815–822
8. Isogai E, Isogai H, Kimura H, Fjii N, Kotake S, Yoshikawa K, Ono S (1999) Establishment of ocular lesion in gnotobiote mice infected by *Streptococcus sanguis* and antibody response against components of the bacteria. An annual report of the Behcet's disease research committee of Japan 1999, pp 40–44
9. Direskeneli H, Hasan A, Shinnick T, Mizushima R, Zee R van

der, Fortune F, Stanford MR, Lehner T (1996) Recognition of B-cell epitopes of the 65 kDa HSP in Behcet's disease. Scand J Immunol 43:464–471
10. Tasci B, Direskeneli H, Serdaroglu P, Akman-Demir G, Eraksoy M, Saruhan-Direskeneli G (1998) Humoral immune response to mycobacterial heat shock protein (hsp) 65 in the cerebrospinal fluid of neuro-Behcet patients. Clin Exp Immunol 113:100–104
11. Hamzaoui K, Ayed K, Slim A, Hamza M, Touraine J (1990) Natural killer cell activity, interferon-gamma and antibodies to herpes viruses in patients with Behcet's disease. Clin Exp Immunol 79:28–34
12. Lee S, Bang D, Cho YH, Lee ES, Sohn S (1996) Polymerase chain reaction reveals herpes simplex virus DNA in saliva of patients with Behcet's disease. Arch Dermatol Res 288:179–183
13. Sohn S, Lee ES, Bang D, Lee S (1998) Behcet's disease-like symptoms induced by the herpes simplex virus in ICR mice. Eur J Dermatol 8:21–23
14. Ota M, Mizuki N, Katsuyama Y, Tamiya G, Shiina T, Oka A, Ando H, Kimura M, Goto K, Ohno S, Inoko H (1999) The critical region for Behcet disease in the human major histocompatibility complex is reduced to a 46-kb segment centromeric of HLA-B, by association analysis using refined microsatellite mapping. Am J Hum Genet 64:1406–1410
15. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Goto K, Nakamura S, Bahram S, Ohno S, Inoko H (1999) Association analysis between the MIC-A and HLA-B alleles in Japanese patients with Behcet's disease. Arthritis Rheum 42:1961–1966
16. Mizuki N, Ota M, Yabuki K, Katsuyama Y, Ando H, Palimeris GD, Kaklamani E, Accorinti M, Pivetti-Pezzi P, Ohno S, Inoko H (2000) Localization of the pathogenic gene of Behcet's disease by microsatellite analysis of three different populations. Invest Ophthalmol Vis Sci 41:3702–3708
17. Gul A (2001) Evidence for linkage of the HLA-B locus in Behcet's disease, obtained using the transmission disequilibrium test. Arthritis Rheum 44:239–241
18. Cohen R, Metzger S, Nahir M, Chajek-Shaul T (2002) Association of the MIC-A gene and HLA-B51 with Behcet's disease in Arabs and non-Ashkenazi Jews in Israel. Ann Rheum Dis 61:157–160
19. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Shiina T, Nomura E, Onari K, Ohno S, Inoko H (2001) HLA-B*51 allele analysis by the PCR-SBT method and a strong association of HLA-B*5101 with Japanese patients with Behcet's disease. Tissue Antigens 58:181–184
20. Chang HK, Kim JU, Cheon KS, Chung HR, Lee KW, Lee IH (2001) HLA-B51 and its allelic types in association with Behcet's disease and recurrent aphthous stomatitis in Korea. Clin Exp Rheumatol 19 [Suppl 24]:S31–S35
21. Paul M, Klein T, Krause I, Molad Y, Narinsky R, Weinberger A (2001) Allelic distribution of HLA-B*5 in HLA-B5-positive Israeli patients with Behcet's disease. Tissue Antigens 58:185–186
22. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Yoshida M, Onari K, Nikbin B, Davatchi F, Chams H, Ghaderi AA, Ohno S, Inoko H (2001) HLA class I genotyping including HLA-B*51 allele typing in the Iranian patients with Behcet's disease. Tissue Antigens 57:457–462
23. Choukri F, Chakib A, Himmich H, Hue S, Caillat-Zucman S (2001) HLA-B*51 and B*15 alleles confer predisposition to Behcet's disease in Moroccan patients. Hum Immunol 62:180–185
24. Kotter I, Gunaydin I, Stubiger N, Yazici H, Fresko I, Zouboulis CC, Adler Y, Steiert I, Kurz B, Wernet D, Braun B, Muller CA (2001) Comparative analysis of the association of HLA-B*51 suballeles with Behcet's disease in patients of German and Turkish origin. Tissue Antigens 58:166–170
25. Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Shiina T, Palimeris GD, Kaklamani E, Ito D, Ohno S, Inoko H (2002) Sequencing-based typing of HLA-B*51 alleles and the significant association of HLA-B*5101 and -B*5108 with Behcet's disease in Greek patients. Tissue Antigens 59:118–121
26. Takeno M, Kariyone A, Yamashita N, Takiguchi M, Mizushima Y, Kaneoka H, Sakane T (1995) Excessive function of peripheral blood neutrophils from patients with Behcet's disease and from HLA-B51 transgenic mice. Arthritis Rheum 38:426-433
27. Lehner T (1997) The role of heat shock protein, microbial and autoimmune agents in the aetiology of Behcet's disease. Int Rev Immunol 14:21–32
28. Kaneko S, Suzuki N, Yamashita N, Nagafuchi H, Nakajima T, Wakisaka S, Yamamoto S, Sakane T (1997) Characterization of T cells specific for an epitope of human 60-kD heat shock protein (hsp) in patients with Behcet's disease (BD) in Japan. Clin Exp Immunol 108:204–212
29. Direskeneli H, Eksioglu-Demiralp E, Yavuz S, Ergun T, Shinnick T, Lehner T, Akoglu T (2000) T cell responses to 60/65 kDa heat shock protein derived peptides in Turkish patients with Behcet's disease. J Rheumatol 27:708–713
30. Ergun T, Ince U, Eksioglu-Demiralp E, Direskeneli H, Gurbuz O, Gurses L, Aker F, Akoglu T (2001) HSP 60 expression in mucocutaneous lesions of Behcet's disease. J Am Acad Dermatol 45:904–909
31. Turan B, Gallati H, Erdi H, Gurler A, Michel BA, Villiger PM (1997) Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Bechcet's disease; soluble TNFR-75 as a biological marker of disease activity. J Rheumatol 24:128–132
32. Hamzaoui K, Hamzaoui A, Guemira F, Bessioud M, Hamza M, Ayed K (2002) Cytokine profile in Behcet's disease patients. Relationship with disease activity. Scand J Rheumatol 31:205–210
33. Frassanito MA, Dammacco R, Cafforio P, Dammacco F (1999) Th1 polarization of the immune response in Behcet's disease: a putative pathogenetic role of interleukin-12. Arthritis Rheum 42:1967–1974
34. Raziuddin S, al-Dalaan A, Bahabri S, Siraj AK, al-Sedairy S (1998) Divergent cytokine production profile in Behcet's disease. Altered Th1/Th2 cell cytokine pattern. J Rheumatol 25:329–333
35. Sohn S, Lee ES, Kwon HJ, Lee SI, Bang D, Lee S (2001) Expression of Th2 cytokines decreases the development of and improves Behcet's disease-like symptoms induced by herpes simplex virus in mice. J Infect Dis 183:1180–1186
36. (1990) Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet 335:1078–1080
37. Kaneko F, Oyama T, Sato M, Yamaguchi A, Otsuka M (1999) Behcet's disease and diseases for its differential diagnosis in dermatology. An annual report of the Behcet's disease research committee of Japan 1999, pp 128–134
38. Kaklamani VG, Kaklamanis PG (2001) Treatment of Behcet's disease–an update. Semin Arthritis Rheum 30:299–312
39. Hamuryudan V, Moral F, Yurdakul S, Mat C, Tuzun Y,

Ozyazgan Y, Direskeneli H, Akoglu T, Yazici H (1994) Systemic interferon alpha 2b treatment in Behcet's syndrome. J Rheumatol 21:1098–1100
40. Azizlerli G, Sarica R, Kose A, Ovul C, Kavala M, Kayabali M, Erkan F, Kural Z (1996) Interferon alfa-2a in the treatment of Behcet's disease. Dermatology 192:239–241
41. O'Duffy JD, Calamia K, Cohen S, Goronzy JJ, Herman D, Jorizzo J, Weyand C, Matteson E (1998) Interferon-alpha treatment of Behcet's disease. J Rheumatol 25:1938–1944
42. Georgiou S, Monastirli A, Pasmatzi E, Gartaganis S, Goerz G, Tsambaos D (1998) Efficacy and safety of systemic recombinant interferon-alpha in Behcet's disease. J Intern Med 243:367–372
43. Boyvat A, Sisman-Solak C, Gurler A (2000) Long-term effects of interferon alpha 2A treatment in Behcet's disease. Dermatology 201:40–43
44. Wechsler B, Bodaghi B, Huong DL, Fardeau C, Amoura Z, Cassoux N, Piette JC, LeHoang P (2000) Efficacy of interferon alfa-2a in severe and refractory uveitis associated with Behcet's disease. Ocul Immunol Inflamm 8:293–301
45. Demiroglu H, Ozcebe OI, Barista I, Dundar S, Eldem B (2000) Interferon alfa-2b, colchicine, and benzathine penicillin versus colchicine and benzathine penicillin in Behcet's disease: a randomised trial. Lancet 355:605–609
46. Hamuryudan V, Ozyazgan Y, Fresko Y, Mat C, Yurdakul S, Yazici H (2002) Interferon alfa combined with azathioprine for the uveitis of Behcet's disease: an open study. Isr Med Assoc J 4 [Suppl]:928–930
47. Calguneri M, Ozturk MA, Ertenli I, Kiraz S, Apras S, Ozbalkan Z (2003) Effects of interferon alpha treatment on the clinical course of refractory Behcet's disease: an open study. Ann Rheum Dis 62:492–493
48. Zouboulis CC, Orfanos CE (1998) Treatment of Adamantiades-Behcet disease with systemic interferon alfa. Arch Dermatol 134:1010–1016
49. Lorenz HM, Kalden JR (2002) Perspectives for TNF-alpha-targeting therapies. Arthritis Res 4 [Suppl 3]:S17–S24
50. Keating GM, Perry CM (2002) Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. Biodrugs 16:111–148
51. Travis SP, Czajkowski M, McGovern DP, Watson RG, Bell AL (2001) Treatment of intestinal Behcet's syndrome with chimeric tumour necrosis factor alpha antibody. Gut 49:725–728
52. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN (2001) Effect of infliximab on sight-threatening panuveitis in Behcet's disease. Lancet 358:295–296
53. Aeberli D, Oertle S, Mauron H, Reichenbach S, Jordi B, Villiger PM (2002) Inhibition of the TNF-pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders. Swiss Med Wkly 132:414–422
54. Illei GG, Lipsky PE (2000) Novel, non-antigen-specific therapeutic approaches to autoimmune/inflammatory diseases. Curr Opin Immunol 12:712–718
55. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G (1993) Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med 177:1675–1680
56. Saylan T, Saltik I (1982) Thalidomide in the treatment of Behcet's syndrome. Arch Dermatol 118:536
57. Hamza MH (1986) Treatment of Behcet's disease with thalidomide. Clin Rheumatol 5:365–371
58. Jorizzo JL, Schmalstieg FC, Solomon AR Jr, Cavallo T, Taylor RS 3rd, Rudloff HB, Schmalstieg EJ, Daniels JC (1986) Thalidomide effects in Behcet's syndrome and pustular vasculitis. Arch Intern Med 146:878–881
59. Grinspan D, Blanco GF, Aguero S (1989) Treatment of aphthae with thalidomide. J Am Acad Dermatol 20:1060–1063
60. Gardner-Medwin JM, Smith NJ, Powell RJ (1994) Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behcet's disease: use of neurophysiological studies to detect thalidomide neuropathy. Ann Rheum Dis 53:828–832
61. Hamuryudan V, Mat C, Saip S, Ozyazgan Y, Siva A, Yurdakul S, Zwingenberger K, Yazici H (1998) Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 128:443–450
62. Kari JA, Shah V, Dillon MJ (2001) Behcet's disease in UK children: clinical features and treatment including thalidomide. Rheumatology 40:933–938
63. Jorizzo JL, White WL, Wise CM, Zanolli MD, Sherertz EF (1991) Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behcet's disease. J Am Acad Dermatol 24:973–978
64. Davatchi F, Shahram F, Chams H, Akbarian M, Nadji A, Gharibdoost F, Chamc C, Jamshidi AR, Soroosh S (1998) Methotrexate for ocular lesions of Behcet's disease. Cohort study on 262 patients. Arthritis Rheum 41 [Suppl]:S356
65. Hirohata S, Suda H, Hashimoto T (1998) Low-dose weekly methotrexate for progressive neuropsychiatric manifestations in Behcet's disease. J Neurol Sci 159:181–185