

Review

Behçet's disease

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Abstract

Behçet's disease is characterized by recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions. The role of the *HLA-B*51* gene has been confirmed in recent years, although its contribution to the overall genetic susceptibility to Behçet's disease was estimated to be only 19%. The production of a variety of cytokines by T cells activated with multiple antigens has been shown to play a pivotal role in the activation of neutrophils. As regards the treatment, anti-tumor necrosis factor alpha therapy has been shown to be effective for mucocutaneous symptoms as well as for sight-threatening panuveitis, although a randomized, controlled trial is required.

Keywords: HLA-B51, neutrophil, T lymphocytes, treatment, tumor necrosis factor alpha

Introduction

Behçet's disease is characterized by recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions. Since vascular manifestations are common in this disease, it is regarded as vasculitis. However, the predominant histopathological features in the inflamed tissues are infiltration of lymphocytes and monocytes, and sometimes polymorph nuclear leukocytes, through small veins without microscopic changes in the vessel walls. Thrombophilia or thrombophlebitis involving small and large veins is also common, whereas arteritis is rare. In these regards, Behçet's disease is unique compared with other vasculitides.

The clinical characteristics of Behçet's disease are the recurrent episodes of remission and the exacerbation of various symptoms. Chronic sustained inflammation in certain tissues is rare. Recurrent uveitis attacks usually result in the loss of vision that affects profoundly the activity of daily life of the patients. The involvement of the vascular system, of the intestinal system, and of the central nervous system is usually life threatening.

The etiology and pathogenesis of Behçet's disease have not been fully clarified. However, recent investigations

have made significant progress in these areas. Moreover, increasing attention has been paid to the effect of anti-tumor necrosis factor alpha therapy in this disease. The present article overviews an update on the etiology, pathogenesis, clinical manifestation, and treatment of Behçet's disease.

Etiology and pathogenesis

Genetics

Behçet's disease has higher prevalence in the countries along the ancient 'Silk Road' from Japan to the Mediterranean region. A number of studies have provided evidence that HLA-B51 is strongly associated with the disease in different ethnic groups [1]. It has been discussed, however, whether HLA-B51 participates in the disease due to a linkage disequilibrium with a nearby gene [2], since the positive ratio of HLA-B51 in Behçet's disease patients is only approximately 60% [3].

Mizuki's group recently proposed that the critical region for Behçet's disease in the human major histocompatibility complex (MHC) gene could be pinpointed to a 46-kb segment between the MHC class I chain-related gene A (*MIC-A*) gene and the *HLA-B* gene [4]. The *MIC-A* gene is a highly polymorphic member of MHC class I chain

(MIC), with more than 20 alleles in terms of amino acid variation in the $\alpha 1$ (exon 2), $\alpha 2$ (exon 3), and $\alpha 3$ (exon 4) domains [5]. *MIC-A* encodes a cell surface glycoprotein that is not associated with β_2 -microglobulin, that lacks a CD8 binding site, and that is conformationally stable independent of conventional class I peptide ligands [5]. *MIC-A* is expressed in a variety of cells, and its expression is regulated by promoter heat shock elements similar to those of *hsp70* genes [5]. Analysis of *MIC-A* genotyping revealed that the frequency of the *MIC-A009* allele, coding the extracellular domains of *MIC-A*, was greatly increased in Japanese patients with Behçet's disease [5]. Stratification and linkage analyses between *MIC-A009* and HLA-B*51, however, disclosed that the real disease susceptibility gene in Behçet's disease is the *HLA-B*51* allele itself. Moreover, *MIC-A009* was found to be strongly associated with HLA-B*51 as well as HLA-B*52, which was not increased in Behçet's disease. It was therefore concluded that the significant increase of the *MIC-A009* allele in the Japanese patients is due to a strong linkage disequilibrium with the *HLA-B*51* allele [5].

Similar findings on the linkage disequilibrium between the *HLA-B*51* allele and the *MIC-A* allele have been reported in ethnic groups other than Japanese patients [6]. It has thus been disclosed that strong association of the *MIC-A* A6 allele of the transmembrane region of *MIC-A* with Behçet's disease results from a strong linkage disequilibrium with the *HLA-B*51* allele.

Twenty-four different *HLA-B*51* alleles (*HLA-B*5101*–*HLA-B*5124*) have now been described. It was therefore possible that there might be disease-specific polymorphisms or mutations within the *HLA-B*51* genes. However, analysis with sequencing of the *HLA-B*51* genes from Behçet's disease patients and from healthy individuals failed to disclose the difference in the exonic nucleotide sequences [7]. Moreover, no disease-specific polymorphisms or mutations within the *HLA-B*51* intronic and promoter/enhancer regions could be associated with Behçet's disease, although there were single nucleotide polymorphisms in these regions both in patients and in controls [7]. These data therefore demonstrated that the *HLA-B* exonic sequence that encodes the *HLA-B*51* allele is the real pathogenic factor in Behçet's disease. This observation in a Japanese population has also been confirmed in different ethnic groups [8].

Gül *et al.* confirmed the genetic linkage of the *HLA-B* gene, but not the *MIC-A* gene, with Behçet's disease using the transmission disequilibrium test [9]. However, the highest contribution of *HLA-B* to the overall genetic susceptibility to Behçet's disease was estimated to be only 19% in an analysis of a small group of multicase families [9]. This is consistent with the fact that the positive ratio of HLA-B*51 in Behçet's disease is approximately 60% [3]. Identification

of other susceptibility loci should thus be required. On the contrary, a lower rate of recombination has been observed within the extended MHC region telomeric to the *HFE* gene, which caused hereditary hemochromatosis, and strong linkage disequilibrium is a feature of this part of the genome [10,11]. Gül *et al.* have provided evidence of a novel susceptibility locus for Behçet's disease at position *D6S285* in 6p22-p23, ~17 cM telomeric to the *HLA-B*51* locus, in a linkage study in 28 multicase Turkish families using highly polymorphic microsatellite markers [12]. The identification of the gene in this novel susceptibility locus will make a great contribution to our understanding of the pathogenesis of Behçet's disease.

As regards non-MHC genes, increasing attention has been paid to the mutation of the *MEFV* gene. This gene is linked to familial Mediterranean fever, which has similarities to Behçet's disease in both epidemiology and manifestations. Some mutations in the *MEFV* gene have been implicated in Behçet's disease, suggesting that they might act as additional susceptibility factors in Behçet's disease [13]. Further studies to delineate the frequency of *MEFV* gene mutations in Behçet's disease patients in Japan, where familial Mediterranean fever is extremely rare, would be important to confirm the association of the *MEFV* mutation with the susceptibility of Behçet's disease.

*HLA-B*51* is currently the only gene that has been shown to be linked with susceptibility to Behçet's disease. No HLA-B*51 restriction of certain peptide antigens has been demonstrated, however, rather obviating the possibility that HLA-B*51 might be involved in antigen presentation. HLA-transgenic animal models are quite helpful to explore the relationship between HLA and disease. The occurrence of spontaneous inflammatory disease was thus demonstrated in transgenic rats expressing HLA-B*27 and human β_2 -microglobulin genes [14]. In this regard, it was interesting that a *HLA-B*5101* heavy chain transgenic mouse was developed [15]. However, the animal did not develop Behçet's disease-like manifestations, although it did show a very modestly increased neutrophil activity following f-Met-Leu-Phe stimulation compared with control mice [15]. It would be also interesting to try to establish transgenic animal models of HLA-B*51 and β_2 -microglobulin in order to explore the role of HLA-B*51 in the pathogenesis of Behçet's disease, since there are some similarities in clinical manifestations between Reiter's syndrome and Behçet's disease.

Immunopathogenesis

The pathergy reaction is a unique feature of Behçet's disease and might be closely related to the pathogenesis. It has been shown that the early pathergy reaction at 4 hours is mediated by neutrophils and lymphocytes without vasculitis, with the rapid accumulation of neutrophils at the needle-prick sites [16]. The dermis at 48 hours of the pathergy

reaction was infiltrated predominantly by mononuclear cells composed mainly of T lymphocytes and monocytes/macrophages, with neutrophils constituting less than 5% of the infiltrating cells [17]. It is thus suggested that hyperchemotaxis of neutrophils might play a role in triggering the reaction, whereas activated T lymphocytes are required for the development of the whole pathergy reaction.

The therapeutic efficacy of cyclosporin A in uveitis of Behçet's disease [18] strongly suggests the involvement of T-cell activation in the pathogenesis of this disease. On the contrary, attention was paid to the role of certain strains of streptococci as an etiologic agent. Patients with Behçet's disease have a significantly higher incidence of tonsillitis and dental caries. Systemic symptoms of Behçet's disease could thus be induced after treatment of dental caries or even by intracutaneous injection of the streptococcal antigens [19]. Accordingly, *Streptococcus sanguis*-related antigens KTH-1 stimulated *in vitro* production of IL-6 and IFN- γ by T cells from patients with Behçet's disease [20]. However, *Escherichia coli*-derived antigens also enhanced the *in vitro* production of IFN- γ by T cells from the patients, obviating the possibility that T-cell hypersensitivity in Behçet's disease might be specific for streptococcus-related antigens [20].

Lehner and colleagues explored the response of T cells from patients with Behçet's disease to mycobacterium 65-kDa heat shock protein (HSP), since it was disclosed that serum IgA antibodies to the mycobacterial 65-kDa HSP were elevated in Behçet's disease and that a number of monoclonal antibodies of the mycobacterial 65-kDa HSP cross-reacted with selected strains of *S. sanguis* [21]. They showed that four peptide determinants within the mycobacterial 65-kDa HSP (and the corresponding human HSP peptides) stimulated significantly higher lymphoproliferative responses in Behçet's disease, as compared with the related disease, unrelated disease, and healthy controls [21]. Lehner and colleagues further characterized that the four mycobacterial 65-kDa HSPs and corresponding peptides from human 60-kDa HSP elicited significant $\gamma\delta$ T-cell responses in Behçet's disease, as compared with controls [22]. They claimed that T-cell recognition of certain 60-kDa HSP peptides by $\gamma\delta$ T cells might be important in the pathogenesis of the disease [22]. Lehner and colleagues also postulated that an immune response to the streptococcal HSP might also be directed to epithelial and other human 60-kDa HSPs, although there was the lack of specificity. It is thus possible that antigens other than these HSP-related peptides might be involved in the pathogenesis of Behçet's disease.

Supporting the role of $\gamma\delta$ T cells in the pathogenesis of Behçet's disease, Freysdottir *et al.* provided evidence for the increased proportion of peripheral blood $\gamma\delta$ T cells in Behçet's disease compared with both recurrent aphthous

stomatitis and healthy controls [23]. These $\gamma\delta$ T cells expressed activation markers, such as CD25, CD69, and CD29, and produced the inflammatory cytokines IFN- γ and tumor necrosis factor alpha (TNF- α) [23].

It has been reported that high numbers of $\gamma\delta$ T cells, predominantly V γ 9V δ 2 T cells producing IFN- γ , were recovered from intraocular fluid of Behçet's disease patients but not from control patients [24]. These V γ 9V δ 2 T cells responded to isopentyl pyrophosphate and related non-peptide prenyl pyrophosphates, but not to 65-kDa HSP [24]. Isopentyl pyrophosphate and related prenyl pyrophosphates are essential metabolites for both prokaryotic and eukaryotic cells [25]. It has therefore been suggested that ubiquitous antigens of microbial origin may trigger cross-reactive autoimmune responses in Behçet's disease [25]. The increase in V γ 9V δ 2 T cells has been also found in the peripheral blood of patients with Behçet's disease [26]. These results, however, do not necessarily indicate the specific activation of V γ 9V δ 2 T cells, since human peripheral blood $\gamma\delta$ T cells mainly express V γ 9V δ 2 [27]. It is thus possible that the increase in V γ 9V δ 2 T cells might simply reflect the larger fraction of this subset within the pool of $\gamma\delta$ T cells.

The $\gamma\delta$ T cells account for only 2–5% of peripheral blood T cells in humans. The importance of $\alpha\beta$ T cells in the pathogenesis of a variety of autoimmune diseases has thus been implicated. In this regard, oligoclonal expansion of peripheral blood $\alpha\beta$ T cells has been demonstrated in 30–50% of patients with Behçet's disease [28,29]. Since most of the T-cell expansions were reduced in correlation with ameliorated disease activity, a possible involvement of antigen-specific T cells in the pathogenesis was suggested [29]. It is probable that antigen-specific T-cell responses might drive an attack of a variety of symptoms in Behçet's disease. Of note, positive skin reactions to streptococcal-related antigens as well as *E. coli*-derived antigens and *Klebsiella pneumoniae*-derived antigens were frequently observed in Behçet's disease [19]. It is thus possible that patients with Behçet's disease might be hypersensitive to multiple antigens rather than to a certain single antigen. In fact, although the oligoclonal T-cell expansions have been reported in an exacerbation phase of Behçet's disease, the recurrent expansion of the same T-cell clone in each attack has not been demonstrated in longitudinal courses of Behçet's disease.

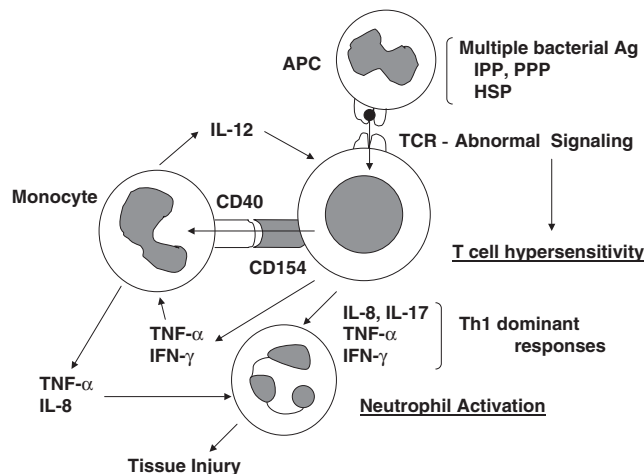
It is postulated alternatively that T cells in Behçet's disease are hypersensitive to a variety of antigens. In this regard, we have demonstrated that T cells from Behçet's disease patients were stimulated to produce IFN- γ with very low concentrations of staphylococcal enterotoxin B and SEC1 that were not able to stimulate T cells from normal individuals or control patients (rheumatoid arthritis) [30]. Since there were no significant differences between

Behçet's disease T cells and control T cells in monocyte-independent or monocyte-dependent IFN- γ production stimulated with low or high concentrations of anti-CD3, it was suggested that abnormalities in signal transduction triggered by perturbation of T-cell receptors, but not in that induced by cross-linking of CD3 molecules, might play an important role in the pathogenesis of Behçet's disease [30]. It should be emphasized that our results do not indicate that the superantigen effects are involved in the pathogenesis of Behçet's disease, but that they emphasize the role of hypersensitive signaling through T-cell receptors. Abnormal signal transduction through T-cell receptors might thus explain the hypersensitivity of $\gamma\delta$ T cells to 65-kDa HSP or to prenyl pyrophosphates. Since monocytes from Behçet's disease patients could not result in hypersensitivity of control T cells to various antigens [30], it is probable that abnormalities in T cells, but not those in monocytes, play a role.

The increased production of IFN- γ has been demonstrated in Behçet's disease. Accordingly, peripheral Th1 cells were significantly increased in active Behçet's disease [31]. Moreover, serum IL-12 levels were found to be correlated with peripheral Th1 cells and disease progression [31], although the mechanism of increased IL-12 production in Behçet's disease remains unclear. Frassanito *et al.* postulated that active Behçet's disease might possibly be a disease of antigen-presenting cells, and that T cells may be 'innocent bystanders', since the elevation of IL-12 appeared to be crucial in the pathogenesis [31]. It should be emphasized, however, that hypersensitivity of T cells that lead to T-cell activation might account for the activation of antigen-presenting cells through CD40-CD154 interactions to produce IL-12. In addition, monocytes from Behçet's disease patients could not result in hypersensitivity of control T cells to various antigens [30]. It would therefore be misleading to conclude that the deviation to Th1 responses in Behçet's disease is due to abnormalities in antigen-presenting cells.

It has recently been shown that active Behçet's disease has a higher number of CD4⁺ T cells containing IFN- γ and CD40 ligand, which are characteristics of Th1 cells [32]. Of note, the elevation of IL-17 in the sera of Behçet's disease has been demonstrated [32]. On the contrary, the production of IL-8, a cytokine that activates neutrophils, by T cells is enhanced in Behçet's disease [33,34]. It should be pointed out that expression of IL-17 has been detected almost exclusively in activated CD4⁺ and CD8⁺ T cells [35]. More importantly, IL-17 has been shown to selectively recruit neutrophils to the sites of inflammation [35]. These results suggest that abnormalities in T-cell responses result in hyperreactivity of neutrophils in Behçet's disease through the production a variety of cytokines, including IL-8 and IL-17. It is therefore strongly suggested that neutrophil activa-

Figure 1



Proposed model of the pathogenesis in Behçet's disease. Ag, antigen; APC, antigen-presenting cells; HSP, heat shock protein; IFN, interferon; IL, interleukin; IPP, isoprenyl pyrophosphate; PPP, prenyl pyrophosphate; TCR, T-cell receptor; Th1, T helper cells type 1; TNF- α , tumor necrosis factor alpha.

tion might be sequelae of hypersensitivity of T cells in Behçet's disease.

The immunopathogenesis that is currently postulated is shown in Fig. 1. Primarily, hypersensitivity of T cells ($\alpha\beta$ T cells and $\gamma\delta$ T cells) to multiple antigens appears to play a critical role in the pathogenesis. The activation of monocytes subsequent to T-cell activation through CD40-CD154 interactions as well as a variety of T-cell-derived cytokines (IFN- γ and TNF- α) may result in the production of IL-12, which leads to the shift to Th1 responses. In consequence of abnormal T-cell activation, neutrophil activation may be triggered by cytokines such as IL-8, IL-17, IFN- γ , and TNF- α . Whereas the roles of costimulation molecules have not been fully explored in Behçet's disease, the presence of anti-CTLA-4 antibody has been reported in a fraction of Behçet's disease patients [36]. Although the presence of this antibody might be possibly involved in abnormal T-cell responses, the antibody might be produced only as a secondary phenomenon of recurrent T-cell activation in Behçet's disease.

Clinical manifestations

Vasculo-Behçet's disease

Involvement of veins and arteries in Behçet's disease is usually called vasculo-Behçet's disease. Venous thrombosis appeared to be the major vascular involvement in 7-33% of patients with Behçet's disease, and represents 85-93% of vasculo-Behçet's disease [35]. Deep vein thrombosis was significantly associated with the male gender and a positive pathergy test [37].

A number of studies have explored the pathogenesis of thrombophilia in Behçet's disease. Neither deficiency in protein C, in protein S, in factor V Leiden and in antithrombin III nor resistance to activated protein C and anticardiolipin antibody levels seemed to be correlated with vascular thrombosis in Behçet's disease [37,38]. There were increased thrombin generation, fibrinolysis, and thrombomodulin in Behçet's disease, but these abnormalities were not related to thrombosis [38]. These results therefore suggest that thrombophilia in Behçet's disease might be related more to inflammation than to clotting disorder.

Recent studies have disclosed the occurrence of anti-endothelial cell antibodies in Behçet's disease [39]. It has been demonstrated, moreover, that increased E-selectin expression was observed when endothelial cells were incubated with sera from patients with active Behçet's disease or with sera from patients with anti-endothelial cell antibodies and high levels of myeloperoxidase, or with purified myeloperoxidase itself [39]. Since neutrophils from active Behçet's disease release increased amounts of myeloperoxidase [39], it is probable that neutrophil activation as well as the expression of anti-endothelial cell antibodies might play an important role in the development of endothelial inflammatory damages, leading to thrombophilia.

Arterial involvement, although rare, does occur in Behçet's disease. The arterial manifestations in Behçet's disease resemble those of Takayasu's arteritis, including arterial occlusion and aneurysm formation. Histopathological studies revealed that the number of vasa vasorum with infiltration of neutrophils and lymphocytes was significantly increased in vasculo-Behçet's disease compared with in Takayasu's arteritis and other inflammatory aneurysms [40]. It was therefore suggested that arterial involvement in vasculo-Behçet's disease might be caused by a neutrophilic vasculitis targeting the vasa vasorum, leading to degeneration of the arterial wall [40].

Neuro-Behçet's syndrome

The neurological involvement in Behçet's disease is either caused by primary neural parenchymal lesions (neuro-Behçet's syndrome) or is secondary to major vascular involvement [41,42]. The latter type is rarely complicated with the parenchymal lesions and should be called vasculo-Behçet's disease [41]. This vasculo-Behçet's disease type generally has a better prognosis compared with the parenchymal type [41].

The most commonly involved area in neuro-Behçet's syndrome is the brain stem, but spinal cord lesions, hemisphere lesions and meningoencephalitis also occur [42]. Among a variety of signs and symptoms, pyramidal tract signs are most frequently observed [41,42]. Although a lot of efforts have been made, the etiology and pathogenesis

of neuro-Behçet's syndrome still remain unclear. In addition, factors determining prognosis and appropriate treatment have not been delineated.

We have recently disclosed that neuro-Behçet's syndrome can be classified as acute type and as chronic progressive type [43]. Acute neuro-Behçet's syndrome is characterized by acute meningoencephalitis with or without focal lesions, presenting high-intensity areas in T2-weighted images or fluid attenuated inversion recovery (FLAIR) images on magnetic resonance imaging scans [43]. Cyclosporin A is frequently associated with acute neuro-Behçet's syndrome, at least among the Japanese patients [44]. Acute neuro-Behçet's syndrome responds to steroid therapy, and is usually self-limiting.

By contrast, the chronic progressive type of neuro-Behçet's syndrome is characterized by intractable, slowly progressive dementia, ataxia and dysarthria, with persistent elevation of cerebrospinal fluid IL-6 activity (>20 pg/ml) [45]. Most patients (approximately 90%) in our series with the chronic progressive type of neuro-Behçet's syndrome were HLA-B51-positive, and they had history of attacks of acute type neuro-Behçet's syndrome prior to the development of progressive neurological symptoms [45].

It should therefore be pointed out that the two types of neuro-Behçet's syndrome are currently considered to represent different stages rather than independent clinical entities. In fact, we have recently experienced some patients who displayed prolonged elevation of cerebrospinal fluid IL-6 activity following the acute type neuro-Behçet's syndrome. It is therefore suggested that the appropriate treatment of such patients can prevent progression of neurological symptoms, although further studies are required to confirm this point. Of note, chronic progressive neuro-Behçet's syndrome is resistant to conventional treatment with corticosteroid, with cyclophosphamide, or with azathioprine. Recent studies, however, suggest the efficacy of low-dose weekly methotrexate in the chronic progressive type of neuro-Behçet's syndrome [46].

Treatment

Abnormal activation of neutrophil functions has been recognized in the pathogenesis of Behçet's disease [47]. Colchicine has been widely used as a basic drug for treatment of Behçet's disease based on the claim that colchicine exerts beneficial effects through inhibition of neutrophil functions [47]. The results of a 2-year randomized, double-blind, placebo-controlled study have recently demonstrated that colchicine significantly reduced the occurrence of arthritis in both female and male patients, whereas it reduced the occurrence of genital ulcers and erythema nodosum only in female patients [48]. This possibly reflects less severe disease among the women [48].

Since T-cell abnormalities have been shown to be involved upstream of neutrophil activation in the pathogenesis of Behçet's disease (Fig. 1), it is conceivable that inhibition of neutrophil functions by colchicine might not be sufficient for treatment of more severe manifestations. In this regard, cyclosporin A, an inhibitor of T-cell function, has been shown to be effective in suppressing an attack of uveitis, one of the most severe manifestations of Behçet's disease [18]. However, the efficacy of cyclosporin A is not still satisfactory in sight-threatening uveitis in Behçet's disease. Moreover, the neurotoxicity of cyclosporin A, which leads to the occurrence of acute type neuro-Behçet's syndrome, has been found in as many as 25.5% of patients [44]. The use of cyclosporin A in Behçet's disease is therefore being limited.

Several groups have reported the beneficial effects of IFN- α in Behçet's disease. Alpsy *et al.* demonstrated, in a 3-month randomized, placebo-controlled, double-blinded study, that IFN- α 2a is effective for the treatment of the mucocutaneous lesions in Behçet's disease [49]. In this trial, five of six patients in the IFN- α 2a-treated group versus one of three patients in the placebo group showed an improvement in ocular manifestations [49]. However, a double-blinded control study with larger numbers of patients would be required to demonstrate the efficacy in the treatment of uveitis in Behçet's disease.

Thalidomide is a drug that virtually disappeared from clinical use after its teratogenicity was demonstrated in the 1960s. The results of a randomized, double-blind, placebo-controlled trial for 24 weeks demonstrated that thalidomide is effective for treating the mucocutaneous lesions, including oral and genital ulcers, and follicular lesions in adult patients with Behçet's disease, although the effect diminished rapidly after discontinuation of treatment [50]. The beneficial effects of thalidomide have also been reported in pediatric patients with Behçet's disease [51]. However, awareness of the danger of axonal neuropathy and teratogenesis at all times during thalidomide therapy is mandatory.

It has been demonstrated that $\gamma\delta$ T cells in Behçet's disease are activated *in vivo* and produce large amounts of TNF- α [23,26]. It has also been shown that thalidomide inhibits transcription of TNF- α [52]. Infliximab, a chimeric monoclonal antibody to TNF- α , has been demonstrated to be an effective therapy for Crohn's disease [53] and rheumatoid arthritis [54]. Accumulating reports on patients with Behçet's disease showed that infliximab was effective in the treatment of intractable orogenital ulceration [55], of skin lesions [56], and of gastrointestinal lesions [57]. It has also been disclosed that infliximab is a rapid and effective therapy for sight-threatening panuveitis in Behçet's disease [58]. Infliximab administration thus leads to a rapid and effective suppression of acute ocular inflam-

mation, and the remission of the uveitis remained for as long as 28 days after infliximab administration in all five patients [58]. Etanercept is also now being used in Behçet's disease. A controlled study with larger numbers of patients for longer periods of time would be required to demonstrate the efficacy of tumor necrosis factor blockade on visual outcome and extraocular manifestations in patients with Behçet's disease.

As mentioned earlier, low-dose weekly methotrexate has been shown to be effective in patients with the chronic progressive type of neuro-Behçet's disease [46]. It has also been shown that methotrexate has beneficial effects in ocular manifestations in Behçet's disease [59]. Further studies to explore the efficacy of methotrexate in various manifestations in Behçet's disease would be worthwhile.

Conclusion

Significant progress has been made in recent years in the etiology and pathogenesis of Behçet's disease. The role of the *HLA-B*51* gene has thus been confirmed, although its contribution to the overall genetic susceptibility to Behçet's disease was estimated to be only 19%. In this regard, identification of a novel gene located in 6p22-p23, telomeric to the MHC region, would be quite important.

The mechanism of neutrophil activation in Behçet's disease was unclear. The results of recent studies have confirmed that the production of a variety of cytokines by T cells activated with multiple antigens plays a pivotal role in the activation of neutrophils. The mechanism of T-cell hypersensitivity and the role of genetic factors need to be clarified. As regards treatment, anti-TNF- α therapy has been shown to be effective for mucocutaneous symptoms as well as for sight-threatening panuveitis in Behçet's disease, although a controlled study with larger numbers of patients is required. Taking into consideration the natural course of Behçet's disease, that the severity of the disease activity declines as years go by after the onset, the use of anti-TNF- α therapy could be limited within several years, thus decreasing the occurrence of adverse effects.

Competing interests

None declared.

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